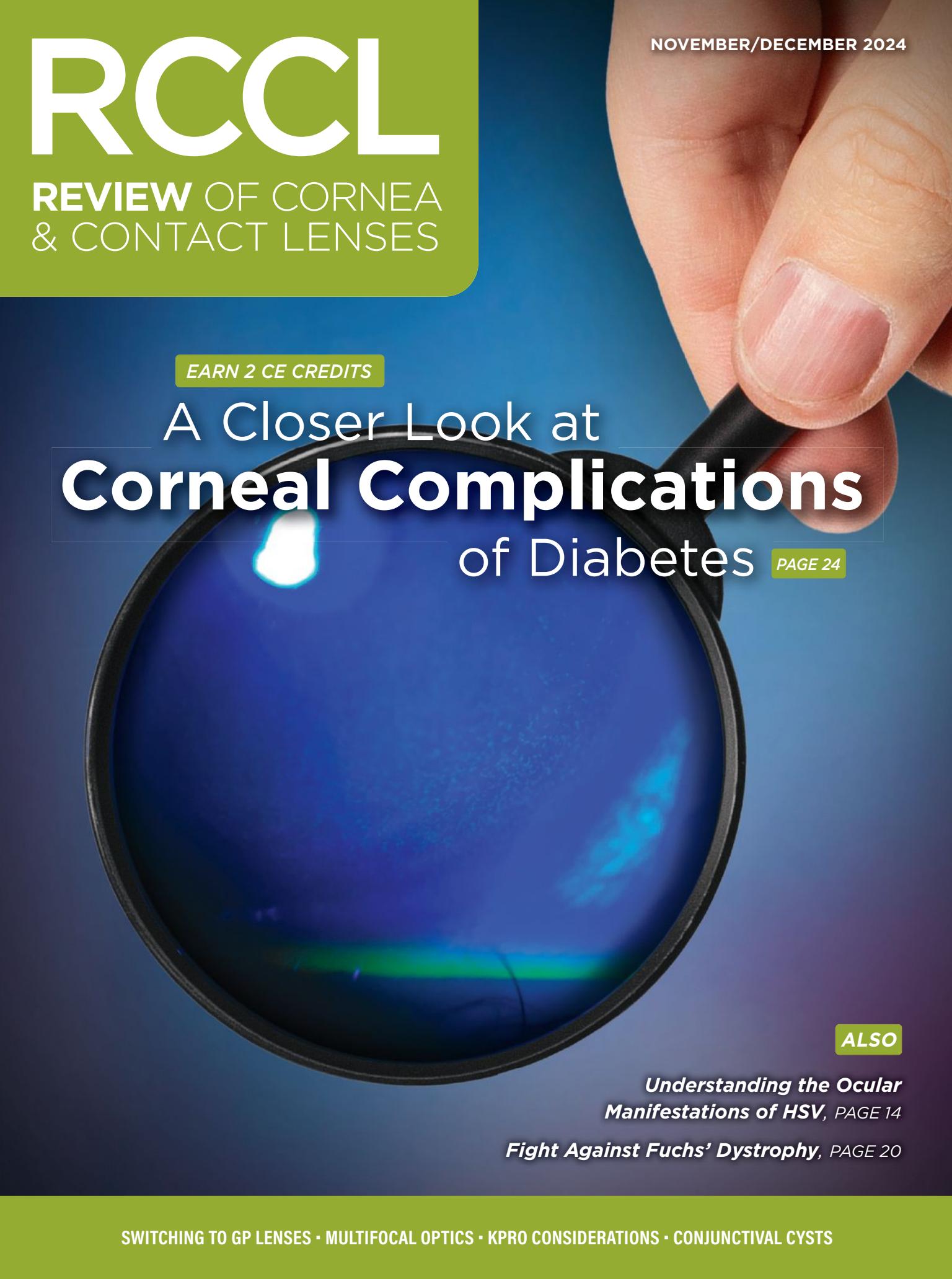
RCCL
REVIEW OF CORNEA & CONTACT LENSES
NOVEMBER/DECEMBER 2024



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One-year Antiviral Course Improves Outcomes for HZO Patients

This new treatment regimen significantly reduced inflammation, pain and disease flare-ups at 12 and 18 months, study finds.

Annually, more than one million people in the US are diagnosed with shingles. Roughly 8% of these patients develop herpes zoster ophthalmicus (HZO) resulting from the impact of the virus on nerve pathways in the eye and forehead, causing significant unilateral pain, redness and impaired vision. While current treatment protocols consist of a seven- to 10-day course of antivirals, new research presented last week at the American Academy of Ophthalmology's annual meeting in Chicago found that extending the treatment duration to 12 months can significantly reduce the risk of ocular inflammation and infection in patients with HZO.

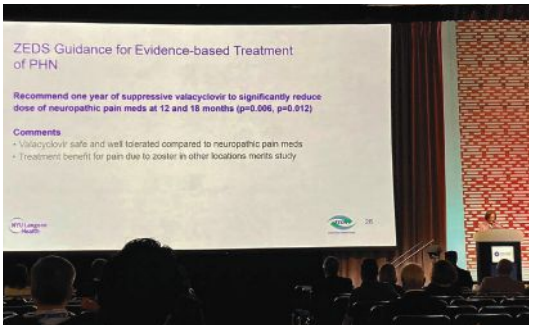
The study was led by Elisabeth J. Cohen, MD, whose career as a cornea surgeon was cut short over a decade ago after she contracted HZO and experienced significant vision loss. Feeling motivated to help find a solution, Dr. Cohen launched an eight-year research effort at NYU Langone Health medical center known as the Zoster Eye Disease Study (ZEDS), which investigated whether one year of treatment with a low dose of the antiviral drug valacyclovir could help reduce pain, ocular complications and disease flare-ups.

The study enrolled 527 participants from the US, Canada and New Zealand who were randomized to receive a one-year course of 1,000mg of Valtrex (valacyclovir, GlaxoSmithKline) or a placebo. Participants were all adults with a functioning immune system and kidneys, history of a typical HZO rash and active keratitis or iritis in the year before enrollment.

The results showed a 26% reduction in the risk of new or worsening eye conditions (keratitis or iritis) at 18 months and significantly fewer flare-ups compared to the placebo group (30% reduction at 12 months and 28% at 18 months). The latter finding is particularly important considering "multiple flare-ups is what goes on to chronic disease and vision loss," Dr. Cohen noted in a recent interview for NYU Langone Health.

Also at 18 months, those on valacyclovir had shorter pain durations and reduced need for neuropathic pain meds.

"Our results support changes in clinical practice, with suppressive valacyclovir recommended to reduce new, worsening and repeated episodes of eye disease, as well as the need for neuropathic pain medication in HZO patients and in those with shingles-related pain," Dr. Cohen told NYU Langone Health.



Prescribing a one-year course of valacyclovir to HZO patients may help mitigate complications associated with the infection, as well as reduce the incidence of flare-ups that contribute to the development of chronic diseases like glaucoma.

IN BRIEF

■ Recent research published in *Ophthalmic Epidemiology* strengthens the link between air pollution and keratoconus. The study, built upon a prior investigation from 2021, analyzed data from 44 studies and **found a positive correlation between fine particulate matter (PM10) and nitrogen dioxide (NO2) levels and the prevalence of keratoconus.**

These findings suggest pollution can affect the cornea both directly and indirectly, the authors noted in their paper, explaining that **"the indirect pathway involves the stimulation of recognized risk factors for keratoconus, such as eye rubbing and atopy. Air pollution is known to reduce the stability and quality of the tear film, but also increase eye irritation and inflammation."**

With keratoconus prevalence varying globally, **the findings underscore the importance of understanding environmental influences on ocular health and disease progression.**

Jurkiewicz T, Marty AS. Air pollution and the prevalence of keratoconus: Is there a connection? Ophthalmic Epidemiol. October 10, 2024. [Epub ahead of print].

■ A new study revealed that **dry eye disease (DED) patients have a higher prevalence of mental health conditions compared to those without DED.** Researchers used the National Institute of Health's All of Us database for a cross-sectional study, identifying 18,257 DED patients. They discovered **significant associations between DED and depressive disorders, anxiety, bipolar disorder and schizophrenia spectrum disorders,** even after adjusting for medical comorbidities. **The link was notably stronger among Black participants.**

The findings **emphasize the need for greater mental health screening in DED patients, especially in underserved populations.**

Zhao AT, He J, Lei Y, Chen Y, Ying GS. Associations between dry eye disease and mental health conditions in the All of Us Research Program. Am J Ophthalmol. October 15, 2024. [Epub ahead of print].

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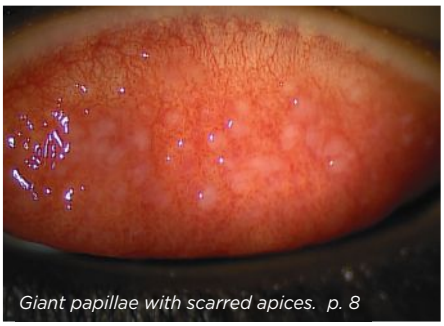
Review of Cornea & Contact Lenses | November/December 2024



Giant papillae with scarred apices. *p. 8*

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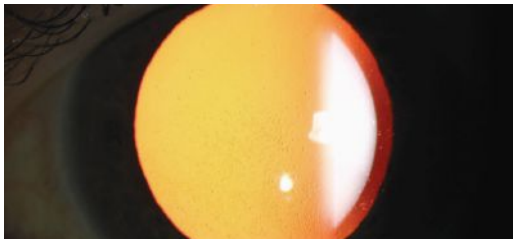

Could it be KC (KERATOCONUS)?

KC File #4: A Troublesome Toric Contact Lens Fit

Bill "Bond" Tullo, OD, FAAO, Princeton, NJ

Dr. Tullo is a paid consultant for Glaukos.

I saw a new patient, a 17-year-old boy. His recently prescribed spectacles were fine—he had no visual complaints—but he disliked wearing glasses when playing soccer and wanted to try part-time contact lens wear. The history and exam were totally unremarkable, other than noting that vision in his left eye wasn't quite as sharp as in the right eye. The patient had no systemic or ocular health issues, no allergies, and was not on any medications.

Insertion and removal training was successful, and I fit him in daily disposable soft toric contact lenses (Precision1 for Astigmatism, Alcon) with a prescription of -2.00 -0.75 x 010 OD and -2.50 -1.25 x 170 OS. He reported good fit and comfort in the office and left happy.

However, at the 1-week follow-up appointment, the patient complained of blurry vision in the left eye and was seeing only 20/25 +1 in that eye. Based on a contact lens over-refraction, we ordered a new lens for the left eye with a slightly different axis (see box). One week after that, the patient returned with similar complaints of blurry vision. Again, an over-refraction suggested a slightly different lens, this time with a lower cylinder correction. Finally, a week later, when the patient returned still unhappy with his vision in the left eye and the over-refraction would have suggested yet a different toric power, I ordered corneal imaging of both eyes.

Left Eye Toric Lens

	LENS	ACUITY AT 1 WEEK	CONTACT LENS OVER-REFRACTION
Attempt #1	-2.50 -1.25 x 170	20/25 +1	+0.25 -0.75 x 145
Attempt #2	-2.50 -1.25 x 160	20/25 +2	Plano -0.50 x 055
Attempt #3	-2.50 -0.75 x 160	20/25 -1	Plano -0.50 x 015

KC File #4: THE CLUES

- ➜ Instability with toric soft lenses
- ➜ Difficulty with refraction in only 1 eye
- ➜ Visual quality complaints
- ➜ Topographic irregularities

Topography/tomography imaging showed irregular astigmatism, abnormal elevation of the posterior cornea, and mild corneal thinning in the left eye, all consistent with a diagnosis of subclinical keratoconus that is worse in the left eye than in the right. This patient is being monitored every 3 months for progression and will likely undergo iLink cross-linking in the future if the keratoconus progresses.

Difficulty in soft toric lens fitting, with shifting refractions and vision that just isn't crisp, is a significant clue that something might be wrong with the cornea. It should not take 3 or 4 lenses to successfully fit a young, healthy patient. However, corneal ectasia causes irregular astigmatism, which makes correction in toric soft contact lenses difficult. I also noticed that this teen was confident and precise when I tested his right eye at the phoropter, but much more hesitant in reading the letters and responding to "Better 1 or 2?" with the left eye. This asymmetry in decision-making was another red flag or clue. I am fortunate to have in-house topography/tomography, but for those who don't, I would encourage a referral for imaging in cases like this. If an immediate referral isn't practical, one might also consider fitting a corneal GP, scleral, or hybrid lens with over-refraction to see if the visual acuity improves. If it does, that is a strong indication of keratoconus and a referral for further corneal evaluation is needed.

By following the KC clues that are hiding in plain sight, you can help young patients get diagnosed and treated earlier, preserving their vision and corneal stability. Visit iDetectives.com to learn more.

#FollowTheClues

iDetective
Following the clues for early KC detection

How to Get Started in Doing Research

Learn how to participate in these opportunities, especially when practicing outside of a university/academic setting.

Our last issue outlined why someone in clinical practice might consider doing research. To briefly review, this expands access to new products and testing capabilities, advances innovation, boosts your knowledge by helping you to stay up to date with developing technology, potentially increases patient retention rates by supporting practice reputation and adds financial compensation. Let's now look at what you can do to enhance your chance of getting noticed and how to take full advantage of those opportunities.

HOW DOES ONE SUCCESSFULLY GET INVOLVED IN RESEARCH?

Here are some insights I've gathered:

1. Find a research mentor. Much depends on where a clinician is in their career and practice setting.[1] It's important to find an influential mentor. I got involved early in my career; our senior partner had been involved in research for decades and was willing to pass on his expertise. Mentors can introduce you to collaborators in the industry.[2] Establish good rapport with industry, starting with company sales representatives. They can convey to the manufacturer's research team who is a good fit for doing marketing studies or even FDA pre-market approval studies.

The ideal clinical investigator mentor must have good communication skills, be organized and have at least some experience with data analysis and statistics.[2-4]

2. Partner with research teams dedicated to handling the logistics.[2] This allows non-university/non-academic providers the luxury of not significantly interfering with clinical duties. The American Academy of Optometry formed a special interest group dedicated to "Fellows Doing Research." Their mission is to pose interesting research questions and how to best go about answering provocative questions through research in clinically based practices. Every other year, the Academy sponsors a "research camp." The program trains interested individuals in the concepts and techniques necessary for multi-centered observational community-based research.[5]

3. Seek adequate training. Clinicians must be willing to undergo the necessary training when accepting a research project. You'll also have to manage audits and inspections.[1]

4. Commit to the necessary infrastructure.[1] This will require a staff member to serve as the study coordinator who will handle the recruitment aspects, schedule visits, complete necessary paperwork, answer patient questions, etc. Remember, study patients generally need longer time slots. Keep things simple for your neophyte team since some trials require a lot of paperwork and time. Compliance with regulatory bodies and sponsor requirements can initially be daunting.[3]

5. Commit to assurance for a suitable, safe study site.[2,3] Secured rooms and storage space are always needed. Necessary equipment might include refrigerators or extra space for storage of study supplies and study data.[1,4]

Depending on your level of participation, there will be several challenges along the journey. With greater involvement, challenges include first developing an appropriate research question, generating adequate data to answer the question with standardized testing, interpreting findings and eventually implementing the findings in clinical practice.[3] If called for, other challenges in human subject studies include working with an institutional review board (IRB) and staying fully engaged throughout the process.[2-4] The IRB ensures that appropriate steps are taken to protect the welfare and rights of participants in a study. Depending on the study design and recruitment requirements and necessary follow-ups, the study sponsor or institution doing the research may provide a centralized IRB.

Take a close look at what's available for those who might be interested in doing research in clinical practice. You may want to start slowly with something like a marketing study sponsored by a product manufacturer and advance as you deem workable for your practice. I would suggest taking advantage of the programs available through our professional organizations, such as "research camps." Should you have any questions on why you might want to do research in clinical practice and how to get started, please share them with us! RCCL

1. Lazas D. Five reasons physicians should integrate clinical trials into their practice. Applied Clinical Trials. www.appliedclinicaltrialsonline.com/view/5-reasons-physicians-should-integrate-clinical-trials-into-their-practice. July 31, 2023. Accessed August 1, 2024.

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When Soft Lenses Go Wrong, Would You Consider Corneal Lenses?

A pivot to this option can often save the day.

I have had a fetw cases recently that have really made me wonder whether a return to fitting more corneal lenses may just improve my doctoring life. For the time being, let's look at patients who just didn't get along with their soft contact lenses. Some of these patients are currently taking a break from lenses as a whole, and others we have managed to refit—either into a different material or modality of soft contact lenses, or, into my personal hero, corneal lenses! In all cases, corneal gas-permeable (GP) lenses are an incredible option to consider, for reasons we will explore.

CASE 1: GIANT PAPILLARY CONJUNCTIVITIS

KH, a 17-year-old African-American young man, developed symptoms of gradually progressive eye irritation over the last 10 months. He reported wear of weekly soft contact lenses for the last five years. He was unsure of the brand or power. He reported using generic multipurpose solution. The average wear time was 12 hours per day, seven days per week, with replacement approximately every two weeks. He reported the entering pair was "about two weeks old" and bothering him. He had backup spectacles but did not bring them to the visit. Medical history was positive for asthma, for which he was not taking any medication. He reported an allergy to amoxicillin.

Slit lamp examination revealed giant papillae in both eyes, graded as 2 to 3+ on the lower lid and 3 to 4+ on the upper lid. Of note, there was apical scarring of the 4+ papillae on the left upper lid (*Figure 1*). The lid was easily everted. The manifest refraction was OD -3.75 -0.50x125 and OS -4.25 -0.50x060. The patient was diagnosed with both giant papillary conjunctivitis OU and floppy eyelid syndrome OU. He was started on a topical steroid and an over-the-counter antihistamine/mast-cell stabilizer. He was also started on nighttime artificial tears ointment with lid taping. Once quiet, this patient would have been a good candidate for refit into a corneal GP lens design.

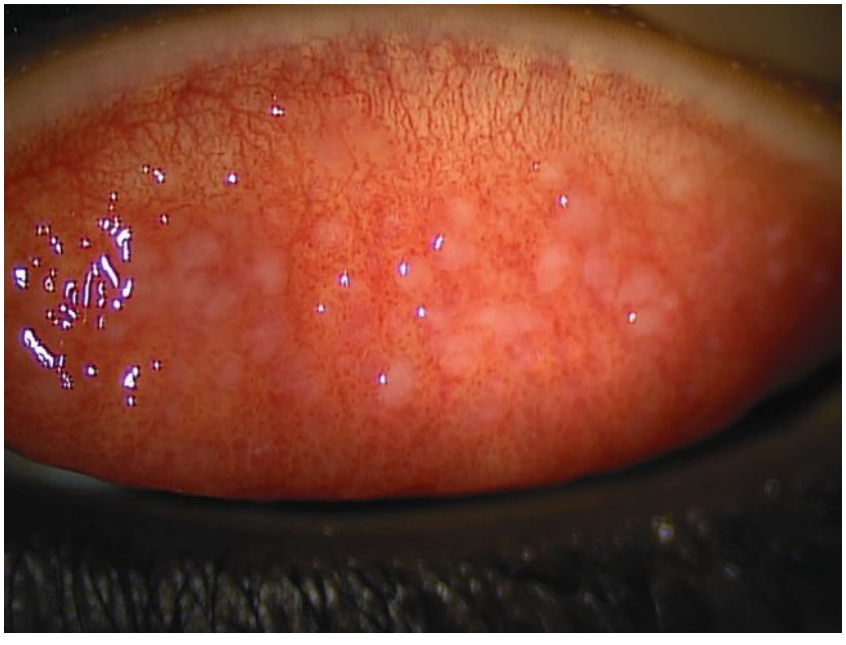

Fig. 1. Upper lid eversion of patient in case 1, showing giant papillae with scarred apices.

CASE 2: LIMBAL STEM CELL DEFICIENCY

MT, a 14-year-old Hispanic girl with degenerative myopia, developed symptoms of gradually progressive discomfort with soft contact lens wear over the last year. She admitted to overwear of her habitual daily disposable multifocal lenses for three or more days at a time. A review of the purchase history indicated that over the past 4.5 years of reported daily wear, the family had purchased a total of 17 months' worth of lenses. She denied being seen at any outside provider or purchasing lenses elsewhere or online during that time.

The patient denied ever sleeping in the lenses. The average wear time was 12 hours per day, seven days per week. She reported the entering pair was new today, from an extra box they had at home. She had backup spectacles but did not like wearing them as she was bullied in class due to their thickness. The patient had no medical conditions and was not taking any medications. She reported no known allergies.

Slit lamp examination revealed a tight-fitting soft contact lens in each

eye with no movement in primary or upgaze. A soft lens push-up test was difficult in each eye. The cornea had limbal neovascularization in all quadrants. Sodium fluorescein staining after lens removal revealed 1+ arcuate conjunctival staining indicating a tight-fitting lens. There were also nasal and temporal punctate epithelial erosions in each eye and a sawtooth staining pattern was identified superiorly at the limbus OU (*Figure 2*).

The manifest refraction was OD -15.75 -3.00x180 and OS -17.00 -0.75x175. A Pentacam scan confirmed corneal warpage was present from the tight-fitting lens in each eye (though it is important to note this type of corneal warpage can masquerade as keratoconus/corneal ectasia). The patient was diagnosed with limbal stem cell deficiency OU due to contact lens overwear. She was started on topical steroids and advised to discontinue wear of her habitual lenses. Once quiet, this patient would have also a good candidate for refit into a corneal GP or scleral lens design to prevent further exacerbation of the limbal stem cells.

CASE 3: CONTACT LENS OVERWEAR

FS, a 53-year-old African-American man with degenerative myopia, developed symptoms of blurry vision and discomfort with a two-year-old pair of monthly replacement, spherical, soft contact lenses. The patient reported he became homeless and was unable to go back to where his lens supply was kept. He also had trouble finding a place to consistently remove and clean his lenses. He instilled artificial tears for contact lenses as needed, which provided some relief to the blur and discomfort. The patient admitted to sleeping in his lenses six or more nights per week. He had a history of both soft toric and scleral lens wear. He denied having any backup spectacles. The patient has a history of heart failure and COPD and is on furosemide 40mg per day. He reported no known allergies.

Slit lamp examination revealed 1+ MGD on the upper and lower lids, 1+ diffuse bulbar conjunctival injection, 2+ palpebral conjunctival papillae and injection, and neovascularization in all quadrants OU (*Figure 3*). There was a faint anterior stromal scar in the right eye, and 2+ diffuse punctate epithelial erosions in each eye after lens removal.

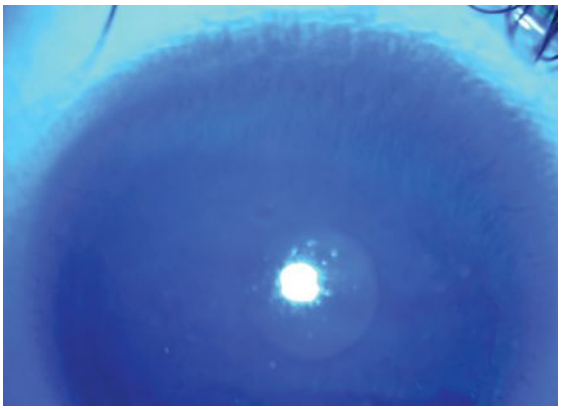

Fig. 2. Superior corneal appearance of patient in case 2, showing sawtooth staining pattern characteristic of limbal stem cell deficiency.

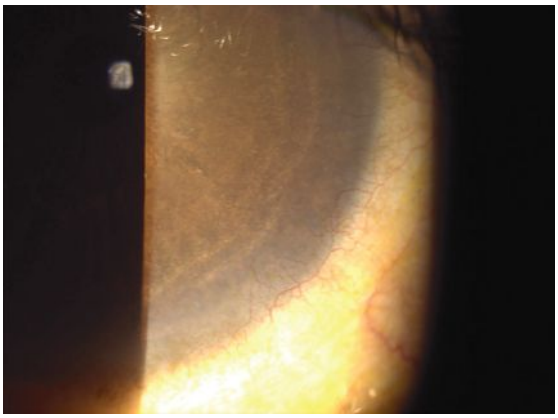

Fig. 3. Corneal neovascularization seen in the patient in case 3.

The manifest refraction was OD -12.00 -2.50x180 and OS -13.00 -3.00x065. He was started on an antibiotic-steroid topical drop, along with preservative-free artificial tears. He was advised to stay out of his contact lenses as much as possible, and a prescription for backup glasses was dispensed.

Once quiet, this patient may have been a good candidate for refit into a corneal GP lens for extended wear in a hyper-Dk material. This would allow him to not only correct all of his refractive error but also allow for flexible wear while preventing worsening of the neovascularization.

Each of these cases presents a soft contact lens fit causing problems for the patient. While short-term lens discontinuation might be wise in these cases, these patients can successfully return to contact lens wear. Often, a well-fitting corneal lens is the answer to help the patient do so in a safe manner for their ocular health.

By Travis M. Pfeifer, OD, Becky Su, OD, and John D. Gelles, OD

Moving the Target

Centering multifocal optics for improved vision in a pediatric patient.

A 10-year-old Asian girl presented to the clinic for orthokeratology (ortho-K) to slow myopia. Her parents reported that her myopia was rapidly progressing. Both parents are high myopes— reportedly over -10.0D. Her entering visual acuity was 20/40-2 OD and 20/40 OS. Her most recent pair of glasses had a prescription of -6.75 -2.25x180 in the right eye and -6.00 -2.00x180 in the left eye.

Entry tests and slit lamp examination were unremarkable. Cycloplegic refraction was -7.50 -2.25x180 and -6.75 -2.00x180 with a best-corrected visual acuity of 20/20 OD and OS. Scheimpflug tomography (Pentacam AXL Wave, Oculus) showed Simulated Ks of 44.7D by 46.4D in the right and 45.1D by 47.0D in left eyes with flat axis of 001 and 179, respectively. Maximum keratometry was 46.8D OD and 47.2D OS; thinnest point was 503 and 490 OD and OS.

Using a multimetric analysis to identify irregular corneas (Belin/Ambrósio Enhanced Ectasia Display (BAD), Oculus) the final D value was 1.54 and 1.90 in the right and left eyes and axial length measurements were 26.18mm and 25.78mm, respectively. Horizontal white-to-white corneal diameter was 12.0mm.

Progressive axial length elongation (PALE) and keratoconus were discussed and treatment was initiated with soft toric center-distance multifocal lenses (Biofinity multifocal toric, CooperVision). On follow-up, the patient complained of poor vision and a laterally displaced position, with unstable rotation being observed.

The decision was made to move to a custom soft toric center-distance multifocal lens—the 54 Bifocal (SpecialEyes)—which was subsequently ordered. Visual acuity improved to 20/25 OU. The stability of vision improved, too, but the visual quality was still poor. To investigate this further, topography (E300, Medmont) over the soft lens was performed to determine the location of the optics, which were found to be bisecting the pupil.

CONSIDERATIONS

Here we highlight our thought process and consider how we would proceed:

Dr. Gelles: This is an interesting case with three issues.

1. Obvious PALE.

2. Poor optical centration of the contact lens.

3. Potential keratoconus.

The corneal findings are very suspicious for keratoconus, with Kmax and the thinnest point falling right at the borderline. The BAD is the result of a multimetric analysis that analyzes anterior elevation, posterior elevation and pachymetry data, synthesizing the data into a single value representing the presence of an irregular cornea. A final D value less than 1.6 is considered normal, between 1.6 and 2.6 is considered suspicious and greater than 2.6 is considered abnormal. Again, here we are right on the borderline for the right eye and suspicious on the left.

As I stated previously in our June/July 2024 column, "Myopia Matters: How to Manage Progressive Axial Length Elongation," the way I approach myopia control is similar to the way a surgeon approaches refractive surgery. If the cornea is normal and the prescription is within reasonable parameters, I will initiate a corneal-based treatment with ortho-K. If the cornea is suspicious, I will initiate a non-cornea based treatment with atropine, defocus soft lenses and/or spectacle lenses, which will preserve the anterior corneal metrics for comparison over time.

In this case, the cornea is suspicious and the refraction is high, thus ortho-K is eliminated as an option. FDA-approved defocus soft lenses to slow PALE (MiSight, CooperVision) are also out due to the high astigmatism. Biofinity's center distance multifocal has a history of being used for myopia control in the BLINK study; it also has a toric option, so it was the natural initial choice for this case.[1] However, the cornea is steeper and slightly wider in diameter than average, contributing to the unstable and off-centered fit.

The change to the custom toric center-distance multifocal soft lens provided much improved stability due to the customized parameters, but the lens was still slightly laterally displaced and the patient experienced poor visual quality. The choice to use a SpecialEyes lens was purposeful, as they have the ability to offset multifocal optics to shift them from the center of the lens to your patient's visual axis (OptiSync Technology, SpecialEyes).

Dr. Su: This case presents some complexities. The patient already shows a high refractive error and an axial length >25mm. More notably, the corneal metrics seen on tomography suggest possible keratoconus, particularly in the left eye. Keratoconus is frequently overlooked in children and often isn't screened adequately. Though this patient

achieves 20/20 with correction, it's crucial to recognize that in pediatric cases not correctable to 20/20, amblyopia might be diagnosed. However, amblyopia is a diagnosis of exclusion and should not be confirmed without evaluating corneal pathology through topography or tomography. It has been reported in the literature that children as young as four years old can have keratoconus, and this can be present with high cylinder and asymmetric astigmatism.[2] Thus, corneal topography is essential.

As a practicing optometrist in Canada with access to myopia control spectacles, this is typically my first-line treatment as it can support corrections up to -10.00D sphere and -4.00D of cylinder. However, if the patient or parents find spectacles challenging due to resistance or an active lifestyle, soft toric lenses would be my next option. When this option is considered, though, it is always advised to have a backup pair of glasses. Ortho-K is contraindicated in this case due to the suspicion of keratoconus. Overnight wear of GP lenses that reshape the cornea could mask the signs of keratoconus, which could lead to a delayed diagnosis. In this case, a custom soft lens with adjustable decentered optics is a great option, as it offers enhanced stability and effective treatment zones not possible with standard soft lenses. Given the corneal conditions and PALE, I would monitor with biometry and topography every three months to track progression in corneal metrics and axial length changes.

Dr. Pfeifer: This can be a tricky case where the priority is to slow down any potential progression in such a young child, but her higher-than-average astigmatism and suspicion of corneal disease complicate the execution of myopia management. Soft toric multifocal contact lenses are often a great first choice of treatment for myopia management in those needing an astigmatic correction. However, decentration can often lead to intolerable reduced vision.

I like to confirm decentration is the cause by manually centering the lenses (using clean fingers) and asking the patient if things are suddenly clearer. Looking at alternative treatment methods, this patient would likely not appreciate clear enough vision in spherical multifocal contacts given her residual astigmatism. Also given the suspicion of keratoconus due to the elevated BAD values OU, I would avoid ortho-K for fear of increasing the likelihood of missing progression.

Avoiding the corneal astigmatism entirely, myopia control spectacles would be a great option; however, I am not yet able to prescribe them here in the US. Similarly, low-dose atropine remains an available option that could be considered. Another interesting option would be a center-distance multifocal bitoric corneal GP, as the refractive and corneal astigmatism match up

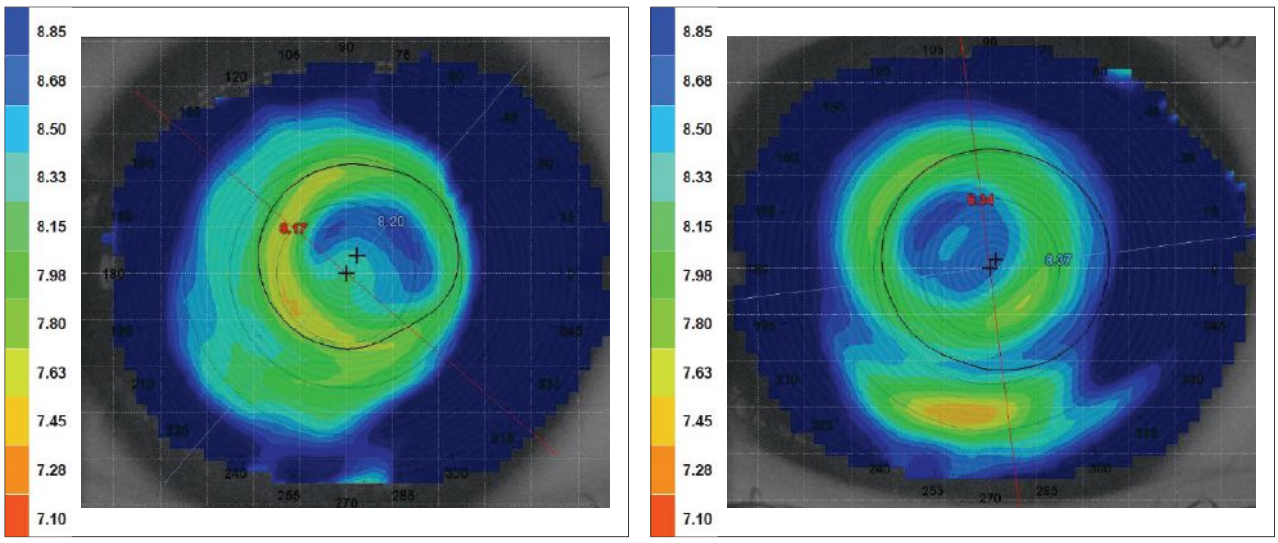

Fig. 1. Over topography of the patient's right eye before (right) and after (left) moving the multifocal position.

By Travis M. Pfeifer, OD, Becky Su, OD, and John D. Gelles, OD

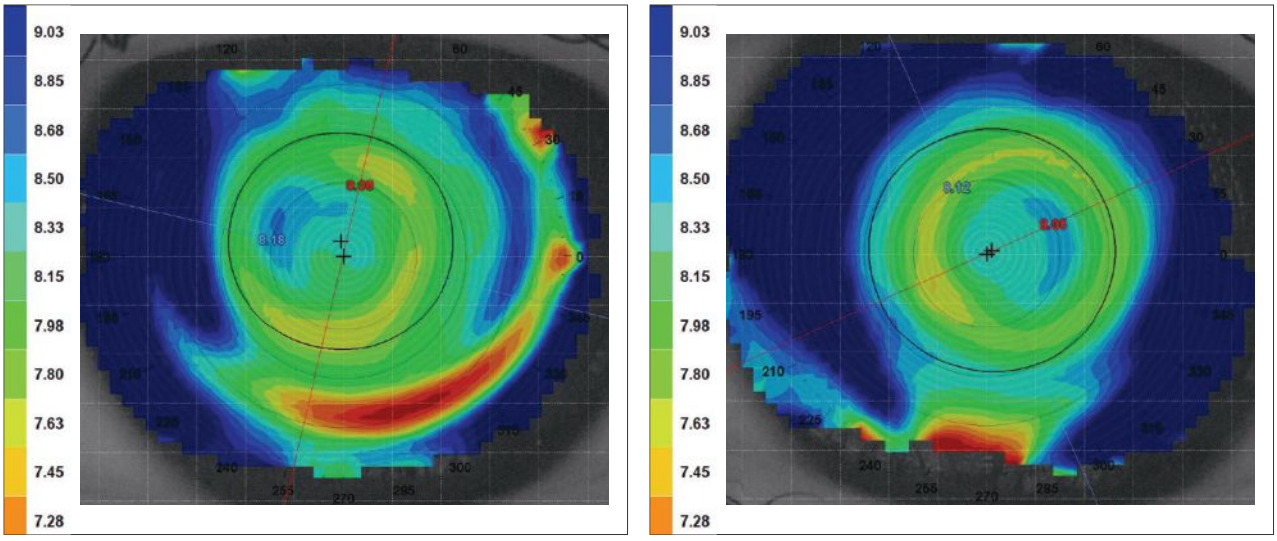

Fig. 2. Over topography of the patient's left eye before (right) and after (left) moving the multifocal position.

very closely. This type of lens may improve visual quality for the patient and can be highly customized to deliver a great amount of peripheral myopic defocus. Some practitioners may find 10-years-old can be young to initiate daily corneal GP wear, but depending on the patient, they may be mature enough to take on some of that responsibility.

Regardless of what treatment modality is chosen, close monitoring of corneal tomography is important for any child for whom corneal disease is suspected. I would opt to monitor the child's myopic progression with axial length measurements as well as monitor for any corneal changes with tomography every three to four months.

DISCUSSION

This case highlights a few critical issues. First is to remember to look before you leap. A recent study sought to determine the prevalence of keratoconus in pediatric patients using Scheimpflug corneal tomography (Pentacam, Oculus). Out of 2,007 subjects aged three to 18, six were diagnosed with keratoconus, for a prevalence of 1:334.[3] This finding suggests that keratoconus is more common in children than previously reported, highlighting the need for early and thorough screening during pediatric eye exams.

Patients are entitled to have more than one problem for us to tackle. We may know PALE is present, but keep keratoconus in the back of our minds as well. As these are both progressive, short interval follow-up every three to four months is prudent. In this case, if keratoconus does manifest, early intervention with crosslinking is necessary. Myopia is a sum of its parts, so ensuring corneal stability and directly measuring axial length is critical.

Poor visual outcomes can be attributed to lens instability or ill-aligned optics. Use of corneal topography over the lens can aid in locating the optical position. Use of the tangential map and a tight scale will allow precise viewing of position, and calipers available on most devices can measure the displacement to the line of sight, which can direct the decentration of optics to the line of sight.

RESULTS

After topography over the lenses, the resulting tangential maps were used to measure the distance between the center of the multifocal optics and the line of sight. The displacement measured approximately 1.0mm and 0.9mm OD and OS, respectively. These measurements were given to the lab and OptiSync was used for the new set. At follow-up the patient reported improved visual acuity. On the tangential map, the shifting of the optics to the line of sight showed an improved optical position (*Figures 1* and *2*) and resulted in improvement in visual acuity to 20/20 OU.

After four-month follow-up, the patient's cornea, axial length and refraction remained stable. The plan now is to follow her every four months to monitor for changes. RCCL

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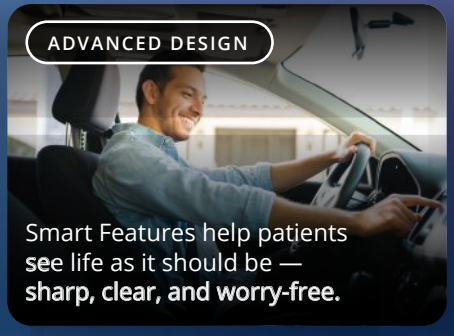

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Understanding the *Ocular Manifestations* of HSV

Accurate diagnosis and management require confident knowledge of the unique ways this disease can present in different layers of the cornea.

BY RAMAN BHAKHRI, OD, JENNIFER HARTHAN, OD, AND WILLIAM SKOOG, OD

Herpes simplex virus (HSV) is an enveloped, linear, double-stranded DNA virus belonging to the Alphaherpesvirinae family, made up of HSV type 1 (HSV-1), HSV type 2 (HSV-2) and varicella zoster virus (VZV); in this article, we will focus on the first two.[1] HSV keratitis is thought to be a leading cause of blindness in developed nations.[2] Diagnosis can be challenging, as the virus can present with a wide range of signs and symptoms. Here, we aim to educate clinicians on the varying clinical presentations and available treatment options to help our patients achieve ideal outcomes.

HSV KERATITIS

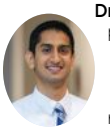
Worldwide, 4.58 billion people (67% of the population) are infected with HSV-1, while 836 million people over age 15 are infected with HSV-2.[3] The global incidence of HSV-1 in 2016 was 2.1%, and the incidence of HSV keratitis was 24.0 per 100,000 persons.[1,4] In the United States, the prevalence of HSV-1 for people between the ages of 14 to 49 is 47.8%, though it has decreased by 11.3% since 2000.[2] It is estimated that nearly 500,000 people in the US have a history of ocular HSV.[1]

Prevalence in the US increases with age, is higher in women and is most common among Mexican-American persons.[2] Improved hygiene practices have contributed to the decline in prevalence by reducing or delaying the risk of exposure, though the latter may lead to more severe illness later in life.[1]

HSV commonly infects the mouth, genitalia and eyes. The virus is spread through direct contact with an infected lesion or secretion as the virus enters the mucous membrane of the host.[5] HSV-1 has a greater association with ocular pathology and HSV-2 is more likely to cause genital infection, but both can infect either location.[6] Once an individual has been infected, the incubation period ranges from one to 28 days. HSV is infectious during asymptomatic shedding and during the five- to 10-day healing process for skin/mucous membrane lesions if they are present.[6] After the primary infection, the virus travels along the sensory nerves via retrograde axonal transport to the trigeminal ganglion where it will remain latent until reactivation.[1] Reactivation can be triggered by fever, hormonal changes, ocular trauma, ultraviolet exposure and stress.[6,7] Reactivation of ocular HSV can cause blepharitis, conjunctivitis, keratitis, uveitis and acute retinal necrosis.

Typically, ocular HSV is diagnosed clinically on slit lamp examination, but diagnostic testing is available including polymerase chain reaction, enzyme-linked immunosorbent assay,

ABOUT THE AUTHORS



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viral cultures, immunofluorescence antibody assay and western blot.[8,9] Western blot has high sensitivity and specificity but is not easily accessible.[9]

HSV keratitis typically presents unilaterally, though bilateral infections can occur in immunocompromised individuals and make up <12% of cases.[8] Presenting symptoms are often vague and include redness, photophobia, discharge, watery eyes, irritation, itching, pain and blurry vision. Therefore, to make an accurate diagnosis, we must rely on clinical signs that vary based on the corneal layer affected (epithelium, stroma or endothelium).[8,10] Below, we'll discuss how HSV keratitis manifests in each of these three layers.

EPITHELIAL KERATITIS

HSV epithelial keratitis is the most common subclassification and first appears as coarse granular epithelial spots that form punctate lesions. The punctate lesions coalesce to form the most common presentation of HSV epithelial keratitis, a dendritic keratitis.[8,11] HSV dendrites present as white, linear, branching corneal dendrites with terminal end bulbs (*Figure 1*).[8,10,12] Using vital dyes is necessary to differentiate HSV epithelial keratitis from other corneal epithelial diseases.

HSV dendrites are true corneal ulcers that stain with fluorescein at the base of the ulcer. The swollen, inflamed epithelial cells that surround the base of the ulcer stain with lissamine green or rose bengal.[8,10] As HSV dendritic ulcers heal, subepithelial haze or ghost dendrites may remain, which lack fluorescein staining.[10] Following resolution of HSV epithelial keratitis, corneal nerve degeneration, decreased corneal sensation, stromal inflammation and/or corneal scarring can persist.[10,13]

STROMAL KERATITIS

Patients with HSV stromal keratitis or interstitial keratitis often have chronic, recurrent inflammation that worsens with each subsequent episode, resulting from retained corneal viral antigens that trigger an antigen-antibody complement cascade.[1,8,10,14] HSV stromal keratitis results from infectious epithelial keratitis or endotheliitis (*Figure 2*).[1,8,10] Clinical manifestations of HSV stromal keratitis include unifocal, multifocal or diffuse stromal infiltrates, stromal edema, an immune ring, corneal thinning and sectoral or diffuse stromal neovascularization.[10,15,16] HSV disease may also present as posterior interstitial keratitis as reported in a case series of five patients.[15]

HSV stromal keratitis may be non-necrotizing or necrotizing in clinical presentation. Non-necrotizing HSV stromal keratitis clinically presents with corneal edema and is often self-limiting. Necrotizing HSV stromal keratitis is rapidly progressive with stromal infiltrates, diffuse inflammation, ulceration and is less responsive to therapy, with corneal perforation possible.[8,10] Both forms of HSV stromal keratitis can be recalcitrant or resistant, leading to vision loss from corneal neovascularization and scarring.[1,10,12,17]

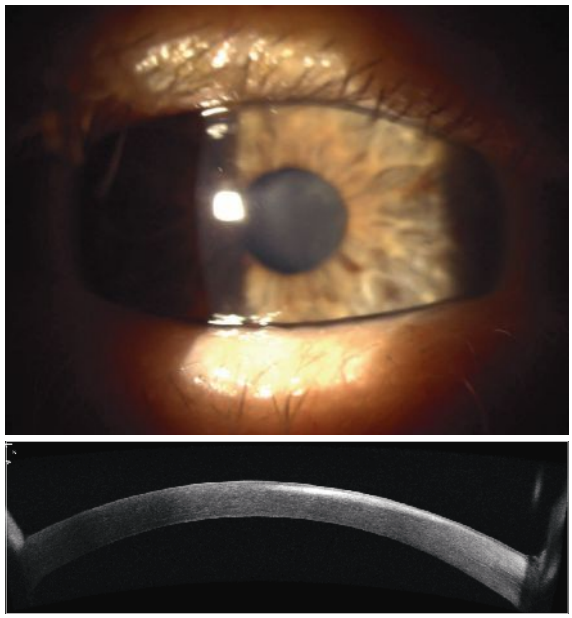

Fig. 2. Same patient from Figure 1 whose epithelial disease resolved with oral antivirals but progressed to stromal keratitis. Top photo shows central stromal haze which corresponds to hyperreflectivity on anterior segment OCT (bottom photo).

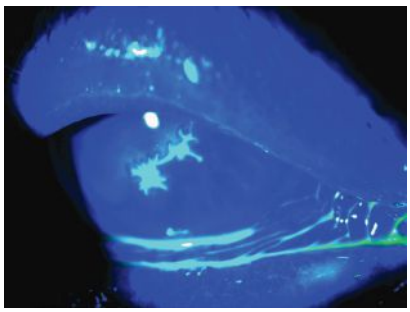

Fig. 1. Typical HSV keratitis epithelial dendrite with terminal bulbs.

ENDOTHELIAL KERATITIS

The clinical presentation of HSV endothelial keratitis will reveal keratitis precipitates, iritis and stromal edema without neovascularization in a disciform, diffuse or linear pattern (*Figure 3*).[8,14] HSV endothelial keratitis, or endotheliitis, is thought to be caused by an active virus in the anterior chamber and can represent an infectious or inflammatory HSV process.[10]

Disciform endothelial keratitis will have a central focal circular area of stromal edema with keratic precipitates and anterior uveitis; it's also the most common presentation.[10] Less common is diffuse endothelial keratitis, which presents as keratic precipitates throughout the entire cornea. Linear endotheliitis is usually the most difficult to treat and will clinically show a distinct linear distribution of keratic precipitates progressing from the limbus, demarcating the involved edematous cornea from the noninvolved

cornea.[10,18,19] Any anterior uveitis with high intraocular pressure should be concerning for possible HSV.

NEUROTROPHIC KERATOPATHY (NK)

This degenerative corneal disease may result from prior episodes of HSV keratitis due to damage to the ophthalmic branch of the trigeminal nerve.[10,20] Diagnosis of NK is based on clinical history, examination and corneal sensitivity testing and can be classified using the Mackie severity scale or the Neurotrophic Keratopathy Study Group Classification.[20-23] Using the Mackie grading system, stage 1 (mild NK) includes corneal epithelial changes; stage 2 (moderate NK) is classified by a corneal epithelial defect; and stage 3 (severe NK) is often characterized by corneal ulceration, perforation and melting.[22,24] Diagnosis of NK can be delayed due to the reduction in corneal sensitivity and, if left untreated, can result in permanent vision loss.[20,25] NK management is targeted to the severity of clinical presentation.[21]

TREATMENT AND MANAGEMENT

As alluded to earlier, HSV keratitis presentation is unique depending on which corneal layer(s) are affected. Once an accurate diagnosis has been made, clinicians have multiple treatment and management options to consider. Below are some evidence-based recommendations.

HSV epithelial keratitis. Two routes of administration are available for clinicians in their management of HSV epithelial keratitis, topical or oral antiviral medications. Although the thought of combining both oral and topical medications in hopes of achieving faster and better outcomes is enticing, the Herpetic Eye Disease Study (HEDS) showed no benefits in this approach.[26,27] Therefore, clinicians should choose one route of administration based on the clinical situation and presentation.

Two topical antivirals (trifluridine solution and ganciclovir gel) and three oral antivirals (acyclovir, famciclovir and valacyclovir) can be used for HSV epithelial keratitis treatment.[27,28] While topical trifluridine is available as a generic ophthalmic solution, we have found that it can be difficult for patients to acquire once prescribed.

Trifluridine is administered at one drop in the affected eye(s) nine times. This excessive dosing schedule along with the presence of thimerosal, a known toxic preservative, can lead to potential corneal toxicity that delays the resolution of keratitis.[29-31] A more convenient option exists with ganciclovir gel, which is administered five times daily until resolution of the keratitis followed by a taper to three times daily for seven days.[32,33] Although both options result in favorable outcomes, ganciclovir may be the preferred choice to trifluridine in certain situations. This applies to patients who cannot instill drops every two hours, those with slow-healing ulcers (trifluridine treatment is restricted to 21 days) and patients under six years old, as trifluridine is only recommended for children older than this age.[27]

Another approach is oral antivirals, which manage HSV epithelial keratitis relatively safely and effectively.[27,34] Dosing depends on the degree of epithelial involvement. HSV epithelial keratitis that is more dendritic in appearance can be managed with a seven- to 10-day course of either acyclovir (400mg five times daily), valacyclovir (500mg three times daily) or famciclovir 250mg (three times daily). If the epithelial keratitis is larger or more geographic, dosing can be extended to 14 to 21 days with the following increase in antiviral strength: acyclovir (800mg five times daily) valacyclovir (1g three times daily) or famciclovir (500mg three times daily).[27,35,36]

While all three agents are safe in most patients, clinicians should remain cautious when prescribing to patients with known kidney disease or those older than 65, as all three have the potential to cause nephrotoxicity, hallucinations, confusion and agitation.[37] Famciclovir is preferred over acyclovir and valacyclovir in elderly patients with or without reduced renal function.[27,38] Consultation with the patient's PCP or nephrologist is strongly suggested before prescribing in such situations. Dosages can also be adjusted based on a patient's renal clearance.

Oral antivirals are often favored over topical antivirals due to their more manageable dosing schedule and lower cost. They are also advantageous for patients who are unable to administer drops or gels, do not respond to topical treatments or have preexisting ocular surface disease.[27,39]

HSV stromal keratitis without epithelial ulceration. Due to a large inflammatory response caused by the HSV virus in the stroma, the HEDS

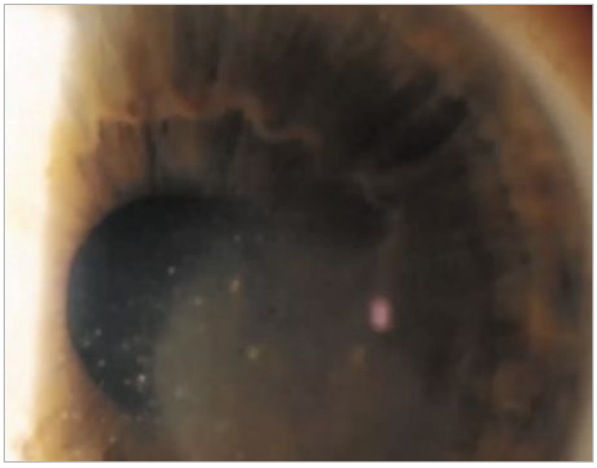

Fig. 3. Stromal haze centrally with keratic precipitation indicative of HSV endothelial keratitis.

Group advised the use of topical steroid therapy in combination with oral antivirals as the mainstay of treatment.[40] A tapered course of topical steroids for more than 10 weeks is suggested, as discontinuation at an earlier stage results in a higher chance of treatment failure.[26] At all times of steroid treatment, the patient should be taking concurrent prophylactic oral antiviral treatment with either acyclovir (400mg two times daily), valacyclovir (500mg daily) or famciclovir (250mg two times daily, or higher doses if indicated). Recommended dosing of topical steroids is prednisolone 1% six to eight times daily, tapered over a time greater than 10 weeks.[27] The ultimate time of the taper period will be determined by the patient's clinical response and appearance of the cornea.[27]

Topical antiviral agents have no role in the treatment of HSV stromal keratitis. Both agents do not adequately penetrate to the corneal stroma when compared to oral antivirals. In addition, they are not indicated for an extended period of treatment time, nor do they address the underlying inflammation.[41,42]

HSV stromal keratitis with epithelial ulceration. As it is rarely encountered, no set treatment protocol has been determined due to the lack of evidence-based clinical studies.[26,40] The American Academy of Ophthalmology Treatment Guidelines suggests a limited dose of prednisolone 1% (twice daily) plus a therapeutic dose of an oral antiviral for seven to 10 days (one of the following, dosed three to five times daily: acyclovir 800mg, valacyclovir 1g or famciclovir 500mg).[27] The oral antiviral can then be reduced to the previously mentioned prophylactic doses with slow taper of the topical prednisolone. Unfortunately, there are no recommendations for the length of treatment.

Fig. 4. Mild epithelial defects can be appreciated here in an atypical fashion.

HSV endothelial keratitis. An uncommon form of HSV keratitis, endothelial keratitis usually presents independent of other forms of HSV keratitis.[27,43] As the inflammation in these cases is further posterior in the cornea, topical trifluridine and ganciclovir again have no role in treatment as they cannot achieve adequate corneal penetration. An oral antiviral agent is therefore needed for corneal penetration.[44] Due to the degree of inflammation seen, anti-inflammatory therapy is indicated. The literature has shown the effectiveness of a combination of a topical steroid in conjunction with an oral antiviral.[36,44] This combination approach leads to healing times between 21 to 25 days.[45,46] Recommended treatment consists of prednisolone acetate 1% every hour or every other hour plus a therapeutic dose of one of the three antivirals. The steroid can be tapered based on the clinical response, while the oral antiviral can be reduced to a prophylactic dose. The length of treatment will again vary between patients.[27]

Clinicians should also be cognizant of prescribing additional treatments including cycloplegic agents to stabilize the blood-aqueous barrier and to immobilize the iris for pain management.[47] With any steroid treatment, intraocular pressure should be monitored for any potential spikes and be managed appropriately with intraocular pressure drops including beta blockers and alpha agonists.[48] Classic teaching states that prostaglandin analogs should be avoided due to their potential links to HSV activation.[27,49] However, this is based on anecdotal case reports or papers based on rabbit models. A larger study found the prevalence of ocular herpes in those using latanoprost (0.11%) to be similar to the general population (0.15%).[50]

REOCCURRENCES: DON'T CALL IT A COMEBACK

Even with prompt and effective treatment, the possibility of recurrence exists in patients with HSV keratitis. As the condition can lead to significant corneal scarring and vision loss, especially in cases of HSV stromal keratitis, clinicians should consider prophylactic or maintenance doses of oral antivirals for their patients.[27]

The HEDS Group examined patients who had an ocular HSV episode in the previous year. Specifically, they looked at the effects of oral acyclovir (400mg twice daily) vs. placebo in preventing ocular HSV recurrences in patients with a history of ocular HSV.[51] The findings indicated that during the 12-month treatment period, the incidence of HSV keratitis recurrences was reduced by half in patients receiving oral acyclovir compared to the placebo group. Additionally, the researchers observed that the protective effect of acyclovir ceased once the medication was discontinued.[51,52]

Importantly, patients who benefited most from prophylactic treatment in HEDS included those with a history of HSV stromal keratitis and those who have experienced multiple episodes of

other types of HSV keratitis (epithelial or endothelial).[51,52] Additionally, clinicians might consider using valacyclovir 500mg daily for prophylaxis, as it has proven to be as effective as acyclovir in preventing recurrences.[53] Another alternative could be famciclovir 250mg taken twice daily, which can be used instead of acyclovir or valacyclovir.[54]

Remember that before beginning any prophylaxis treatment, appropriate communication with a patient's primary physician and other medical specialists is recommended. Renal function should be checked regularly (every six months) with prolonged use of any oral antiviral.

TAKEAWAYS

HSV is one of the most ubiquitous infections clinicians will encounter, capable of affecting any or all layers of the cornea. Through a comprehensive corneal examination, clinicians can determine what type of HSV keratitis they are dealing with and initiate prompt and appropriate treatment to achieve ideal visual outcomes. RCCL

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FIGHT AGAINST FUCHS' DYSTROPHY

Recent advances in understanding genetic infuences may help manage this condition.

By Marcus R. Noyes, OD

Fuchs' dystrophy, a progressive corneal ailment, is characterized by the gradual deterioration and eventual demise of endothelial cells, leading to a significant reduction in their number and functionality. This decline in corneal endothelial cell density disrupts the pump mechanism responsible for maintaining corneal hydration. As a result, excess fluid accumulates in the cornea, leading to corneal edema. The buildup of fluid causes the cornea to swell, resulting in blurred and distorted vision.[1,2]

The underlying cause is not fully understood; however, it is believed to involve a complex interplay of both genetic and environmental factors. Several genes have been identified as potential contributors to Fuchs' dystrophy. Notably, there seems to be a higher risk of the disease among individuals with a family history of the condition. This suggests that genetic predisposition plays a role in its development.[1,2]

Environmental factors are also believed to contribute to the onset and progression. Oxidative stress, which occurs when there is an imbalance between the production of free radicals and the body's ability to neutralize them, is thought to play a role in the deterioration of endothelial cells. Additionally, excessive exposure to ultraviolet (UV) radiation, particularly from the sun, may also damage the corneal endothelium, further contributing to the disease process.[1,2]

It is important to note that Fuchs' progresses slowly and typically affects individuals over the age of 50. The rate of progression and severity of symptoms can vary greatly between individuals. While there is no cure, there are treatment options available to alleviate symptoms and manage the condition. First-line treatments include topical distillation of hypertonic saline, topical steroids or artificial tears. This helps to reduce corneal swelling and improve vision. Moderate-to-severe Fuchs' may require corneal transplantation, which involves replacing the affected cornea with a healthy donor cornea. There are many different methods, including Descemet's stripping automated endothelial keratoplasty (DSAEK), Descemet's membrane endothelial keratoplasty (DMEK) and others.[1-3]

Regular monitoring is crucial to assess the condition's progression and determine the appropriate treatment approach. By closely managing the condition, it is possible to preserve vision and maintain a good quality of life for those affected by Fuchs' dystrophy.

SYMPTOMS AND PROGRESSION

The endothelium plays a crucial role in maintaining corneal clarity and hydration. In the early stages of Fuchs' dystrophy, the endothelial cells gradually decrease in number and function; this can lead to corneal swelling and various symptoms.[1,2,4] As the disease progresses, the following symptoms may appear:

Blurred vision. This is the most common symptom. Because the endothelial cells are unable to pump excess fluid out of the cornea efficiently, blurred vision is often worse in the morning due to overnight fluid accumulation in the cornea.

Glare and halos. Increased sensitivity to light and the appearance of halos around lights are also common symptoms. This occurs because the irregular shape of the swollen cornea scatters light, causing visual disturbances.

Pain or discomfort. In advanced stages, corneal erosions or bullae (fluid-filled blisters) can develop on

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the corneal surface, causing significant pain, discomfort and vision problems.

Decreased visual acuity. Reduced sharpness and clarity of vision are more common symptoms, especially in low-light conditions. This is because the swollen cornea affects the way light enters and focuses on the retina, resulting in decreased visual acuity.

The progression of Fuchs' dystrophy varies from person-to-person and is influenced by several factors, including age, genetics and environmental factors such as exposure to ultraviolet radiation and smoking.

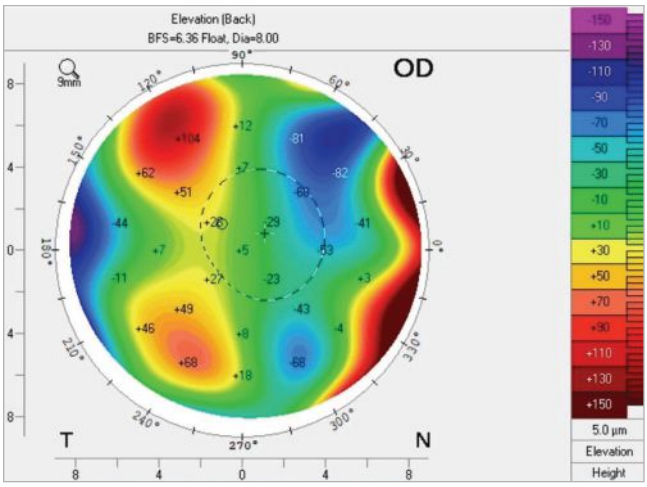
IMPACT ON HIGHER-ORDER ABERRATIONS (HOAs)

These are optical imperfections in the eye that can significantly impact the quality of vision, even in individuals with normal visual acuity. HOAs cause distortions, such as glare, halos and decreased contrast sensitivity, particularly in low-light conditions.[4]

The fluid accumulation in the cornea associated with Fuchs' dystrophy alters its shape and refractive properties, leading to an increase in HOAs. This can further exacerbate the visual symptoms, making it challenging for patients to see clearly, especially in low-light conditions.[4]

Recent studies have investigated the relationship between Fuchs' dystrophy and HOAs. These studies have consistently demonstrated a significant increase in HOAs in individuals with the condition compared to healthy individuals. The increase in HOAs was particularly pronounced in the early morning when corneal edema is typically most severe. Furthermore, the studies showed that the increase in HOAs correlated with the severity of the disease, suggesting that HOAs may serve as a potential biomarker for monitoring disease progression.[4]

Theses findings highlight the importance of considering HOAs in the management of Fuchs' dystrophy. By understanding the impact of HOAs on vision, clinicians can better tailor treatment strategies to address the specific visual needs of individuals with Fuchs' dystrophy. Additionally, monitoring HOAs over time is now possible with aberrometry and can provide valuable insights into disease progression and help guide treatment decisions.[4]



A patient with Fuch's dystrophy showing focal areas of swelling superotemporal and inferotemporal.

Further research is needed to explore the potential of HOAs as a diagnostic tool for Fuchs' dystrophy and to investigate the impact of various treatment modalities on HOAs. This research may lead to the development of more effective treatments, ultimately improving the quality of life for individuals affected by this condition.

DIAGNOSIS

A comprehensive eye examination is needed to make a diagnosis, which typically includes the following:

Slit-lamp examination may reveal corneal guttae on the endothelium, which can appear white or pigmented.

Corneal tomography may show irregular astigmatism and is also sensitive to intracorneal swelling by measuring pachymetry or back surface elevation (as the cornea will thicken with corneal swelling).

Endothelial cell count imaging measures the density of endothelial cells in the cornea. It can also provide qualitative analysis on the size and shape of the endothelial cells. Patients with Fuchs' dystrophy will often show decreased endothelial cell count, along with pleomorphism and polymegethism with this type of imaging.[1]

GENETICS

While the exact genetic mechanisms are not completely understood, research has identified several key genes and chromosomal regions implicated in its development:[1-2]

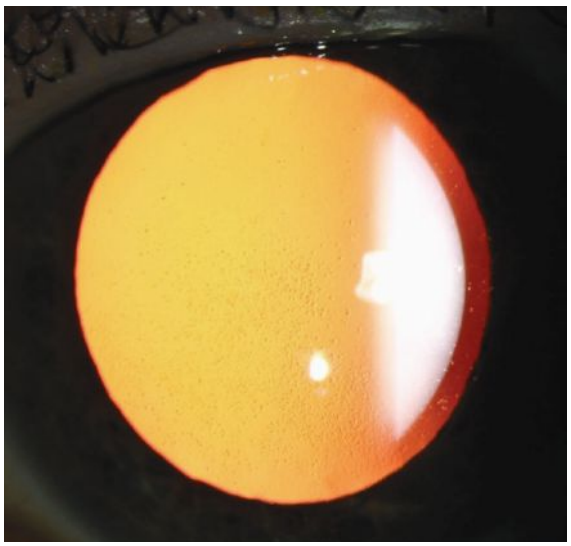
TCF4: This gene is the most frequently associated with Fuchs' dystrophy, particularly in individuals of Caucasian descent. A specific mutation within this gene accounts for a significant proportion of cases.

COL8A2: Mutations in this gene are linked to an early-onset variant of Fuchs' dystrophy, characterized by more rapid progression and the formation of corneal bullae. This gene is responsible for the production of type VIII collagen, crucial for supporting the corneal endothelium.

SLC4A11: This gene codes for a sodium borate cotransporter, and its mutations have been identified in individuals with late-onset Fuchs' dystrophy. The exact role of this gene in corneal health is still under investigation.

ZEB1: This gene is involved in cell differentiation and has been associated with Fuchs' dystrophy in some studies.

Inheritance patterns. Fuchs' dystrophy can be inherited in an autosomal dominant pattern, meaning that only one copy of the mutated gene is sufficient to cause the condition. This



Retroillumination slit lamp photo showing corneal guttae.

is particularly evident in cases linked to COL8A2 mutations.

In some families, the inheritance pattern remains unclear, suggesting that other genetic or environmental factors may be involved. There are also documented cases that arise from spontaneous mutations, occurring in individuals with no family history of the disease.[1-2]

MANAGEMENT

Antioxidant therapy is a promising approach to counteract oxidative stress in Fuchs' dystrophy. These compounds neutralize reactive oxygen species, reducing oxidative damage and preserving cellular function. Topical application of antioxidant agents to the cornea may help protect endothelial cells from oxidative stress. For example, N-acetylcysteine is a precursor to glutathione and has been explored for its ability to enhance the antioxidant capacity of corneal endothelial cells. Systemic administration of antioxidants such as vitamins C and E, alpha-lipoic acid and coenzyme Q10 may provide broader protection against oxidative damage.

Mitochondrial dysfunction plays a central role in Fuchs' dystrophy-related oxidative stress. Compounds such as mitoquinone (MitoQ) specifically target the mitochondria to reduce reactive oxygen species (ROS) production and improve mitochondrial function. These targeted therapies may offer more precise protection for endothelial cells.[1,2]

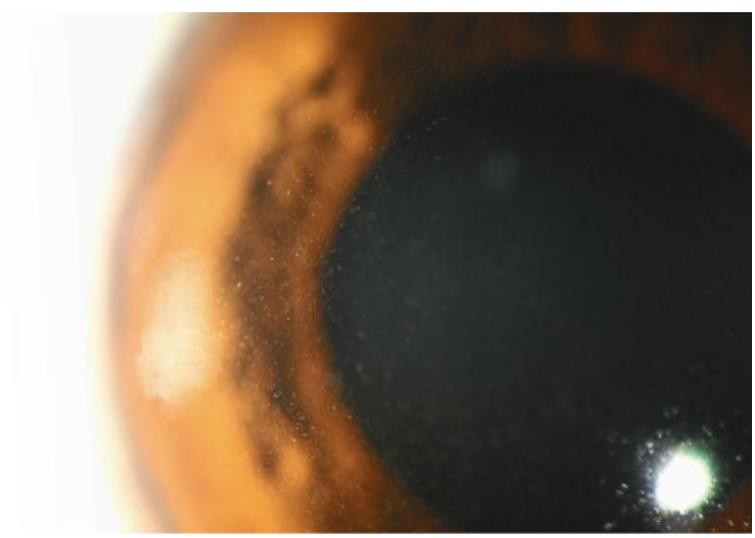
Advances in the genetic understanding of Fuchs' dystrophy offer potential for gene therapy approaches aimed at reducing oxidative stress in endothelial cells. Therapies targeting the TCF4 gene or other genetic contributors may help modulate the stress response pathways and enhance cellular resilience to oxidative damage. Gene editing (such as CRISPR/Cas9) allows for precise correction of genetic mutations, such as those in the TCF4 gene. Correcting these mutations could improve the oxidative stress response in endothelial cells, potentially halting or slowing disease progression.[1,2]

Several pharmacological agents targeting oxidative stress and cellular protection are being explored. Rho-kinase inhibitors have shown promise in promoting endothelial cell survival and reducing oxidative damage, which may enhance endothelial cell resilience and improve corneal clarity in patients with early-stage disease.[1,2]

One recent advancement is the development of a novel ubiquinol/γ-cyclodextrin (γ-CD) complex to improve the solubility, stability and delivery of ubiquinol for ophthalmic applications. Ubiquinol, the reduced form of coenzyme Q10, is a potent antioxidant known to suppress ferroptosis, a form of cell death driven by iron-dependent lipid oxidation. However, ubiquinol's poor water solubility and instability have hindered its therapeutic application.[5]

The authors conducted molecular docking studies, enabling a significant portion of ubiquinol's hydrophobic tail and head group characterized by both hydrogen bonding and hydrophobic forces, contributing to the complex's stability. They found the following[5]:

Enhanced stability. Complexed ubiquinol demonstrated significantly higher stability in various aqueous media relevant to ophthalmic use, including: corneal transplant storage mediums, intraocular irrigation solution and artificial tears—compared to free ubiquinol.



Slit lamp photo showing corneal guttae.

Improved ROS scavenging. The complex effectively lowered ROS levels in both lung epithelial cells, a model with high basal ROS production and human corneal endothelial cells. This effect was more pronounced with the complex, rather than with free ubiquinol.

Inhibition of lipid peroxidation and ferroptosis. The complex effectively inhibited ferroptosis in cells. Importantly, the complex completely protected these cells from erastin-induced ferroptosis, while free ubiquinol did not. Similar results were observed with RSL3, another ferroptosis inducer.

Enhanced corneal penetration. The authors demonstrated that the complex facilitated transcorneal penetration, enabling delivery to the corneal endothelium. Similarly, the ubiquinol complex showed superior penetration and higher retention in the corneal endothelium compared to free ubiquinol in both topical application and storage media models.

It was concluded that the ubiquinol complex holds great promise for various ophthalmic applications, including:

Preservation of donor corneal tissue. Supplementing corneal storage media with the complex could improve the viability and quality of donor corneas, potentially increasing tissue availability and transplant success rates (oxidative stress is considered a major factor contributing to cell death and decreased graft survival).

Treatment of Fuchs' dystrophy. As a topical therapy, the complex could help protect corneal endothelial cells from oxidative damage, potentially slowing disease progression and reducing the need for corneal transplantation.

This research highlights the potential of using cyclodextrin complexes to improve the delivery and therapeutic efficacy of ubiquinol. Further research is needed to determine the optimal dose and long-term effects of this novel formulation in clinical settings.[5]

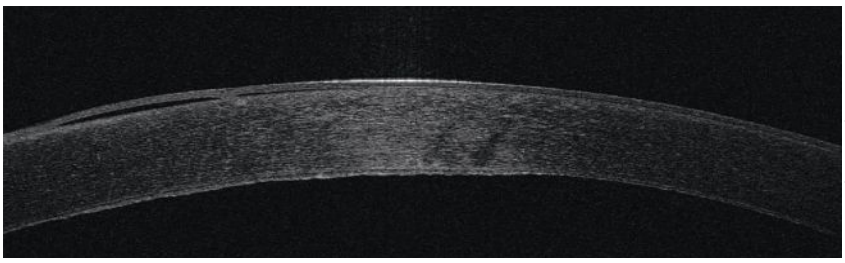


Photo: Christopher Lopez, OD

Anterior segment OCT shows the irregular corneal endothelium in a patient with Fuchs' dystrophy.

LIFESTYLE MODIFICATIONS

Reducing exposure to environmental factors that exacerbate oxidative stress may also be beneficial in managing Fuchs' dystrophy. UV radiation is a known source of oxidative stress in the eye. Wearing UV-blocking sunglasses and avoiding excessive sun exposure may help reduce the oxidative burden on corneal endothelial cells. A diet rich in antioxidants including leafy greens, fruits and nuts, may help support the body's natural defenses against oxidative stress. Systemic administration of antioxidants such as vitamins C and E, alpha-lipoic acid and coenzyme Q10 may provide broader protection against oxidative damage by improving the overall redox state of the body.[2]

SURGICAL OPTIONS

These treatments aim to replace the damaged endothelial cells that maintain corneal clarity. DMEK is the preferred technique, replacing the diseased Descemet's membrane and endothelium with a healthy donor graft. This method offers excellent visual outcomes and faster recovery with low rejection rates. DSAEK replaces a slightly thicker layer of the cornea and may be suitable for patients who aren't ideal candidates for DMEK. Penetrating keratoplasty, a full-thickness corneal transplant, is rarely used for Fuchs' dystrophy now, and comes with the longest recovery time.

There is also a newer, less invasive option being studied called Descemetorhexis without Endothelial Keratoplasty, where the diseased Descemet's is removed to allow healthy cells to regenerate, but long-term outcomes are still being evaluated.[1,3]

TAKEAWAYS

While the exact cause remains elusive, a complex interplay of genetic and environmental factors is thought to contribute to Fuchs' onset and progression. The disease's hallmark is the gradual loss of corneal endothelial cells, leading to corneal edema and visual impairment. Fortunately, recent advancements in research offer a glimmer of hope. The development of a novel ubiquinol formulation shows promise in protecting corneal endothelial cells and potentially slowing disease progression. This, coupled with ongoing genetic research and the exploration of new drug therapies, signifies a turning point in the fight against Fuchs' dystrophy. As these promising avenues continue to be explored, the future holds the potential for improved treatment options and enhanced outcomes for individuals affected by this challenging condition. RCCL

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Corneal Complications of Diabetes: What ODs Need to Know

Given the significant impact this condition has on a patient's quality of life, optometrists must have a comprehensive understanding on the potential ocular involvement.

By Kamila Mikos, OD

Diabetes mellitus, with its ever-growing prevalence, is one of the most common systemic diseases eyecare providers encounter. The International Diabetic Federation estimates that close to 537 million adults worldwide are living with diabetes, including 51 million in North America alone.[1] The consequences of this chronic, metabolic disorder are well studied, including microvascular changes, nephropathy, retinopathy and neuropathy. These complications can severely impact a patient's quality of life by increasing their morbidity and mortality. Most notably for eyecare providers, diabetes is the leading cause of blindness in the United States.

While ocular complications of diabetes tend to focus on diabetic retinopathy, the anterior segment of the eye is frequently overlooked. We are learning that the cornea and ocular surface are also significantly affected by diabetes; however, these complications are often underdiagnosed. Estimates suggest that approximately 70% of patients suffer from corneal complications.[2] Therefore, a comprehensive approach to fully assess the ocular health in diabetic patients is crucial to manage the sequelae of this condition.

UNDERSTANDING PATHOGENESIS

Hyperglycemia, the formation of advanced glycation end products, and oxidative stress result in a variety of anterior segment complications, including defective corneal epithelial healing, subbasal corneal nerve abnormalities and dysfunction of the corneal endothelial pump.[3]

Research shows that diabetes leads to an upregulation of insulin-like growth factor-binding proteins. These proteins compete with insulin-like growth factor, which plays a critical role in corneal wound healing and cell proliferation. When insulin-like growth factor becomes less available, epithelial cell damage occurs due to dysregulation. This can manifest as chronic epithelial defects that may result in recurrent erosions or delayed wound healing.

Oxidative stress and the accumulation of reactive oxygen species play a role in corneal cell damage and inflammation. Chronic inflammation perpetuates a cycle of damage, affecting corneal epithelial cells and nerves, which are important in proper wound healing and regeneration.[3,4]

TEAR FILM DYNAMICS

Essential for a healthy cornea, tears prevent infection, flush away debris and unwanted particles, keep the cornea moist and hydrated and create a protective cushion between the cornea and the environment. Hyperglycemia and the increase of advanced glycation end products can cause damage to the lacrimal gland, causing decreased tear production. Additionally, reduced corneal sensitivity, commonly seen in diabetic patients, can compromise tear production by diminishing the tear reflex, which consequently reduces reflex-induced lacrimal secretion and the production of basal tears.[3]

Not only can tear film quantity be affected, but the components of the tear film in diabetic patients may not also be working cohesively. Mucin, which is important in forming the glycocalyx that adheres the tear film to the cornea, is secreted by our corneal and conjunctival epithelial cells. Studies show that goblet cells, important for maintaining the mucin layer, can be reduced in patients with diabetes.[5,6] When conjunctival cell damage occurs, this layer can be

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Dr. Mikos is an assistant clinical professor at SUNY College of Optometry, where she serves as the attending doctor in various clinical settings including retina, anterior segment, dry eye, cataract and primary care. She earned her Doctor of Optometry degree from SUNY College of Optometry and completed her residency in ocular disease at SUNY College of Optometry and Woodhull Hospital. In addition to teaching and supervising clinical interns and residents, Dr. Mikos actively participates in scholarly activities with a focus on ocular disease and has presented at national conferences. She is a member of the American Academy of Optometry. She has no financial disclosures.

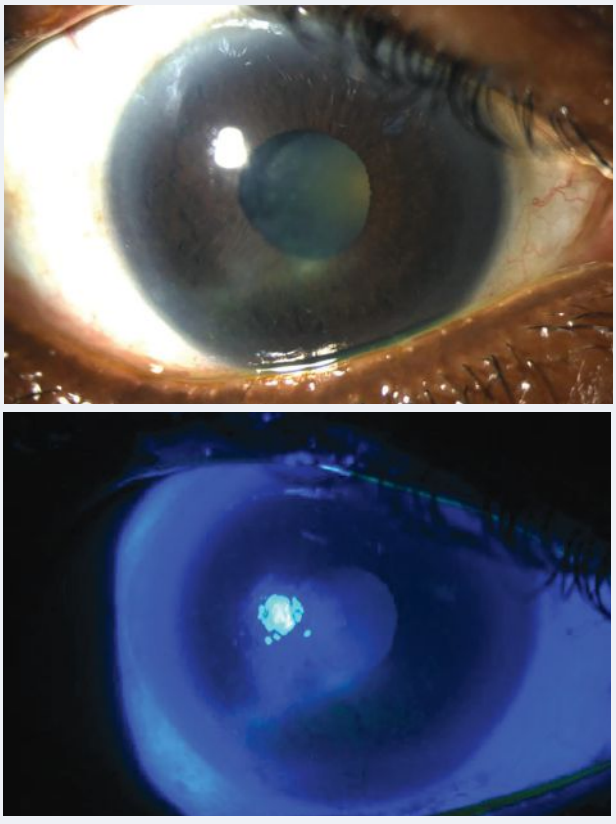

Fig. 1. (A) Neurotrophic keratitis in a 78-year-old woman with uncontrolled type 2 diabetes for 20 years, A1c 11%, proliferative diabetic retinopathy OU seen in white light and (B) under cobalt blue filter.

compromised, promoting friction and increasing the likelihood of damaging the fragile corneal epithelium.

The lipid layer of the tear film, which is important for preventing tear film evaporation, has been shown to be compromised in this patient population as well. The changes in the meibomian glands did not correlate to changes in symptoms score on the Ocular Surface Disease Index (OSDI) survey, possibly due to the changes in corneal sensitivity. The lipid layer may also be disrupted due to decreased corneal sensitivity, which reduces the blink rate and causes increased evaporation.[7]

Other factors in the tear film have been studied in relation to diabetes. Studies show increased matrix metalloproteinases and tear osmolarity in diabetic patients. Matrix metalloproteinases are an inflammatory marker found in the tear film, which may be increased due to hyperglycemia triggering inflammatory cascades that promote ocular surface disease. They can delay wound healing and promote anti-collagenase activity as well. Similarly, tear hyperosmolarity is seen more frequently in diabetic patients, propagating the inflammatory cascade as well.[4]

CORNEAL EPITHELIUM

Substance P, an important neuropeptide that is a crucial component of neuronal support to the cornea, has been shown to be reduced in the tear film of diabetic patients. Lower levels of substance P can lead to decreased nerve fibers and impaired corneal wound healing. A fragile epithelium and weakened adhesions between the epithelium and the basement membrane complex put patients at a higher risk for epithelial defects, corneal erosions and infections.

One of the ways this translates for eyecare providers is an increased risk of contact lens-related complications in diabetic patients. They are more susceptible to contact lens-induced epithelial damage, reduced hydration and oxygen exchange and infectious keratitis. This can lead to issues ranging from increased contact lens discomfort to serious microbial keratitis; therefore, caution should be used when fitting diabetic patients.[8]

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Other clinical considerations include refractive surgeries such as laser-assisted in situ keratomileusis (LASIK) and photorefractive keratectomy (PRK). These procedures are a relative contraindication in patients with diabetes due to poorer refractive outcomes and epithelial complications, which occur in about 50% of cases.[9]

Since PRK involves removal of the epithelium, this can be problematic in patients that have impaired epithelial healing. LASIK may be preferable as it involves only creating a flap and applying laser directly to the stroma; however, it still causes epithelial damage, putting patients at higher risk of complications like epithelial ingrowth.[2,10,11] Other factors to consider are damaged sensory nerves and goblet cells, which are already compromised in diabetic patients. These procedures may still be performed with caution while being particularly careful in patients with a high HbA1C or uncontrolled glucose control.

CORNEAL STROMA

The limited research on the corneal stroma in diabetic patients shows that collagen fibril crosslinking increases in response to hyperglycemia and the accumulation of advanced glycation end products. This is further exacerbated in patients with poor glycemic control and patients with proliferative diabetic retinopathy and can lead to an increase in central corneal thickness.[12]

CORNEAL ENDOTHELIUM

Hyperglycemia leads to the accumulation of sorbitol and advanced glycation end products that may cause endothelial cell decompensation. This can result in decreased endothelial cell density, polymegathism (increased cell size and variation of size of cells) and pleomorphism (decrease in hexagonality of cells).[13]

One way to assess the corneal endothelium in clinic is through an endothelial cell count to pick up on these changes. Increased central corneal thickness may also be observed on pachymetry due to endothelial cell loss and increased collagen crosslinking in the stroma, leading to increased thickness and stiffness of the cornea. This has implications for patients, particularly after cataract surgery, where the endothelium's role in maintaining corneal transparency and fluid regulation can be compromised.

Diabetic patients are more likely to suffer from postoperative complications such as corneal edema following cataract surgery.[14] The endothelium—which is responsible for corneal deturgescence via regulating fluid transport—can be compromised in diabetic patients. Coupled with the mechanism trauma of the surgery, this can cause corneal edema, decreased visual acuity and a lack of transparency of the cornea.

Studies have shown that patients with diabetes account for 80% of cataract and refractive surgery corneal complications.[4] Evaluation of the corneal endothelium is recommended prior to cataract surgery, especially in patients with uncontrolled diabetes.[4]

CORNEAL NERVES

Systemic neuropathy, associated with both type 1 and type 2 diabetes, is a hallmark of the disease, affecting about 50% of patients.[5] The cornea, being one of the most innervated

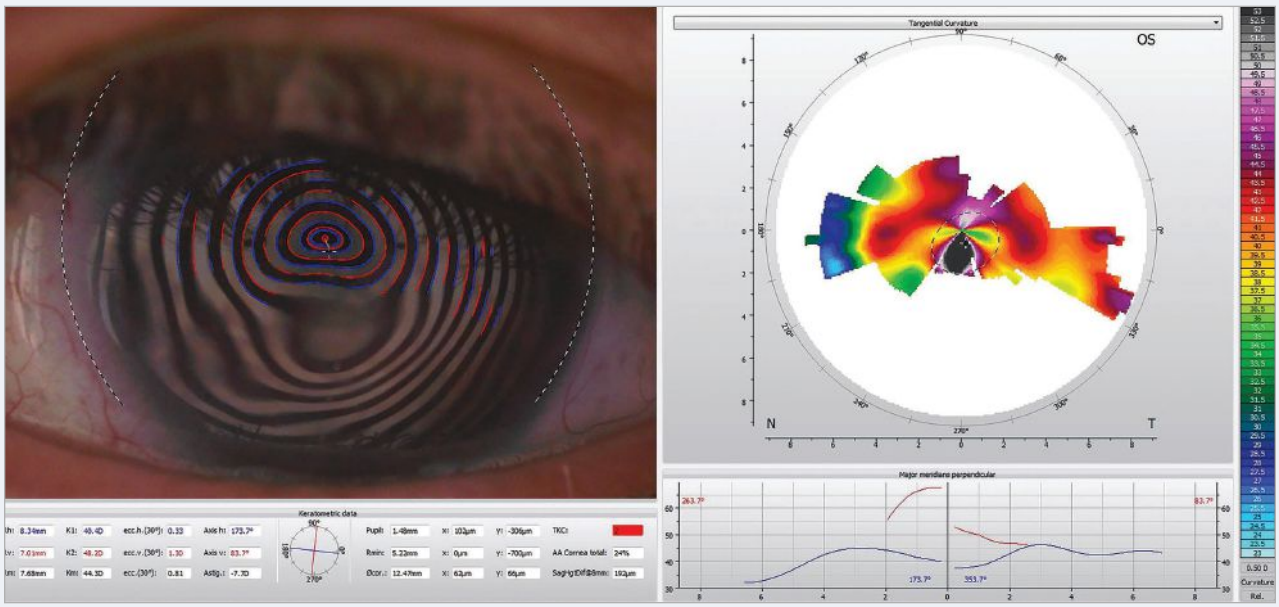

Fig. 2. Induced irregular astigmatism in a 70-year-old woman with neurotrophic keratitis. One treatment option for this patient is scleral contact lenses.

organs in the body with the highest density of nerve fibers, is understandably affected by diabetes.

Chronic hyperglycemia can cause damage to the trigeminal nerve, resulting in a loss of corneal innervation. The corneal nerves provide sensory feedback to help promote epithelial cell proliferation, blink reflex and tear production. This occurs via the neurotrophic role of the nerves because of neuromediators, such as nerve growth factor.

Nerve growth factor is crucial for epithelial regeneration and maintaining neuronal health through the promotion of neuronal repair mechanisms by secreting a variety of neuropeptides, growth factors and cytokines. In a hyperglycemic state, such as in diabetics, we see decreased neuromediators (*i.e.*, nerve growth factor) that play an important neurotrophic role in promoting proliferation of corneal epithelial cells and maintaining corneal homeostasis.[15] This causes decreased corneal innervation, epithelial cell breakdown and delayed wound healing. Therefore, the corneal nerves have two downstream effects—direct impact on the nerves themselves and on the corneal epithelium.[16]

Eyecare providers should recognize the neurotrophic component of dry eye disease. This can lead to neurotrophic keratitis, a condition that is divided into three stages. The first stage is characterized by punctate corneal epithelial defects that are superficial. Stage 2 is more severe, resulting in persistent epithelial defects, often in the classic oval-shaped epithelial defect with "rolled edges."

Stage 3 neurotrophic keratitis is characterized by stromal involvement, leading to ulceration, stromal melting and eventually corneal perforation. This stage is more challenging to manage, which is why it is critical to identify this disease in its earlier phases. Interestingly, patients may not have any symptoms at all, except for blurred vision, due to decreased corneal sensation, sometimes referred to as "stain with no pain."

Beyond neurotrophic keratitis, changes in the corneal nerves among diabetic patients can induce neuropathic pain.[17] This condition is characterized as persistent ocular pain without significantly visible signs on clinical examination and is sometimes referred to as "pain without stain."

Hyperglycemia, ocular surface disease and various factors are thought to increase sensitization of the peripheral neurons innervating the cornea.[16,17] This results in increased central sensitization over time, where the central neurons become highly responsive to a similar magnitude of pain, even when the peripheral stimulus is taken away. The spontaneous activity translates as a pain sensation and causes heightened awareness of overall pain.

CONSIDERATIONS FOR DIAGNOSIS

Optometrists can be more apt at catching anterior segment complications of diabetes by incorporating certain testing for these patients as well as those with dry eye. Corneal nerve testing should be considered as part of a dry eye workup, particularly when a patient's symptoms do not align with the signs seen on clinical examination.

A simple, qualitative test to perform in-office involves testing corneal sensitivity to check for a reduced blink response. One can take a cotton wisp, dental floss or thread to check a patient's blink reflex. Patients with a reduced or absent blink reflex likely have reduced corneal sensation.

While typically used in research, esthesiometers, such as the Cochet-Bonnet esthesiometer or the Belmonte esthesiometer, are an option for more quantitative tests. The Cochet-Bonnet uses a nylon monofilament with a constant diameter to quantify how much pressure is needed to elicit a blink response. The Belmonte esthesiometer is a noninvasive option, using air puffs of various pressures, temperatures and concentrations of carbon dioxide to assess corneal mechanical, chemical and thermal sensitivity, respectively. The Brill esthesiometer is a great handheld alternative for practitioners. It has shown consistent repeatability and is a non-contact option for testing corneal sensitivity in-office.[18]

In addition to corneal nerve testing, sodium fluorescein dye can help measure tear break-up time. Checking for epithelial defects is crucial in these patients. Schirmer's tests can be useful for the assessment of reduced basal tearing when used with anesthetic. Without anesthetic, Schirmer's tests can evaluate both reduced basal and reflex tearing.

Studies have shown that patients with diabetes have significantly lower tear break-up time and Schirmer test values compared with non-diabetic patients.[6] Tear osmolarity and inflammatory markers tend to be elevated in diabetic patients; therefore, ODs should consider tests such as InflammaDry (Quidel) or TearLab (Trukera/Bausch + Lomb).

In cases where neuropathic pain is suspected, particularly when a patient has minimal signs of dry eye on examination, the proparacaine challenge test is a quick diagnostic tool. If a patient reports little to no improvement in symptoms after the instillation of proparacaine, the patient may have some central sensitization of their pain or hyperalgesia, as the peripheral stimulus has been removed.

TREATMENT AND MANAGEMENT

Effective management of corneal sequelae of diabetes begins by emphasizing the importance of tight glycemic control. Studies imaging the corneal nerve plexus have shown an increase in the density of nerves with

improvement of HbA1C, suggesting that lower HbA1C levels are associated with corneal nerve regeneration.[19]

Due to prolonged wound healing in diabetic patients, more aggressive dry eye treatments are necessary to promote corneal re-epithelialization. Providers should be aggressive with lubricants, including artificial tears and ointments; however, they should avoid preservatives that can exacerbate the condition. Punctal plugs should be used with caution with ocular surface inflammation, as the retention of inflammatory markers in the tear film may worsen dryness.[20] Optometrists should also consider eye masks and eye shields to promote healing at night.

Therapeutic bandage contact lenses may help patients with persistent epithelial defects and recurrent corneal erosions. These lenses act as a barrier for the cornea, block friction from the eyelid and allow epithelial cells to adhere to each other. Another option is scleral lenses, which can create a barrier and lubricate the cornea constantly by allowing it to bathe in a reservoir of fluid. They also help correct any irregular astigmatism secondary to corneal complications. The FDA recently approved the PROSE lens (Prosthetic Replacement of the Ocular Surface) for therapeutic use for patients with corneal dystrophies and degenerations.[21] This device, similar to a scleral lens, helps treat underlying ocular surface disease while improving vision.

Prophylactic topical antibiotic treatments should be considered for patients with persistent epithelial defects. It is strongly recommended to use this treatment with therapeutic contact lenses to decrease infection risk. Systemic antibiotics, particularly tetracyclines, can be considered for prophylaxis since they have the added benefit of helping inhibit matrix metalloproteinases that promote inflammation and help prevent collagen degradation.[22]

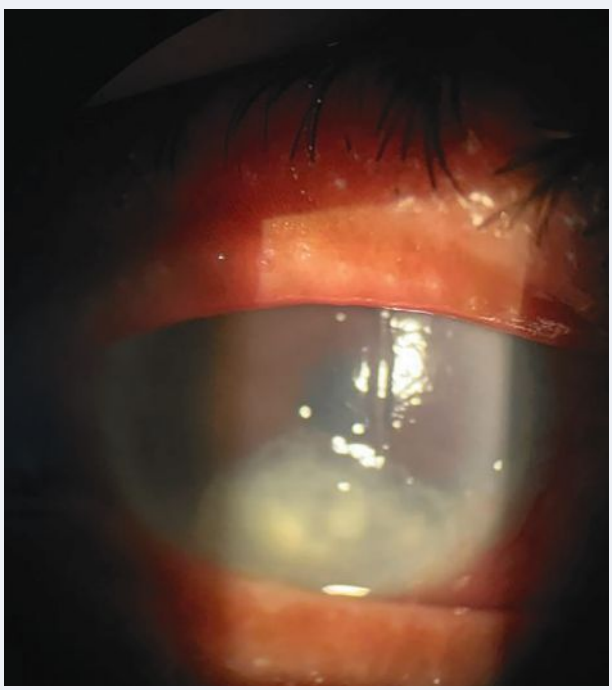

Fig. 3. Neurotrophic ulcer (stage 3 neurotrophic keratitis) in the right eye. There is an overlying epithelial defect with classic rolled edges in the inferior third of the cornea and underlying stromal haze.

Autologous serum contains a variety of factors, such as vitamin A, growth factors and anti-inflammatory factors, that help with epithelial healing and nerve regeneration. Amniotic membranes, like cryopreserved or dehydrated, provide similar factors important for cell and nerve regeneration while also acting as a scaffold to promote corneal healing.

In the last few years, Oxervate (cenegermin-bkbj 20mcg/mL, Dompé), a topical medication, has been FDA-approved for treating the root cause of neurotrophic keratitis. Cenegermin is a recombinant human nerve growth factor, structurally similar to the human nerve growth factor responsible for promoting nerve and corneal regeneration. This novel medication has been shown in trials to stimulate corneal epithelial cell proliferation and differentiation as well as help with tear secretion.

The REPARO and NGF0214 trials demonstrated complete corneal healing in 72% of patients after an eight-week course of Oxervate that was sustained in 80% of patients 48 weeks (about 11 months) post treatment.[23,24] Additionally, the study demonstrated improved corneal sensitivity and tear film production. This therapy aims to address the underlying cause of neurotrophic keratopathy, including cases secondary to diabetes.

For patients with neuropathic ocular pain, there are a variety of potential treatment options. Autologous serum drops and amniotic membranes have components, such as nerve growth factor, that aid in nerve regeneration to help alleviate symptoms. Since inflammation is believed to contribute to this condition, anti-inflammatory treatment, including a pulse dose with topical steroids or cyclosporine drops for more long-term use, can be beneficial.

Systemic pharmacotherapy has been used for central sensitization. Studies show that therapies, such as tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs) and anti-epileptic medications (*i.e.*, pregabalin and gabapentin), have some efficacy in alleviating symptoms in patients with neuropathic pain.[15]

Severe cases may require surgical intervention. For instance, recurrent corneal erosions may necessitate phototherapeutic keratectomy, amniotic membrane transplantation, surgical tarsorrhaphy or even corneal trans-

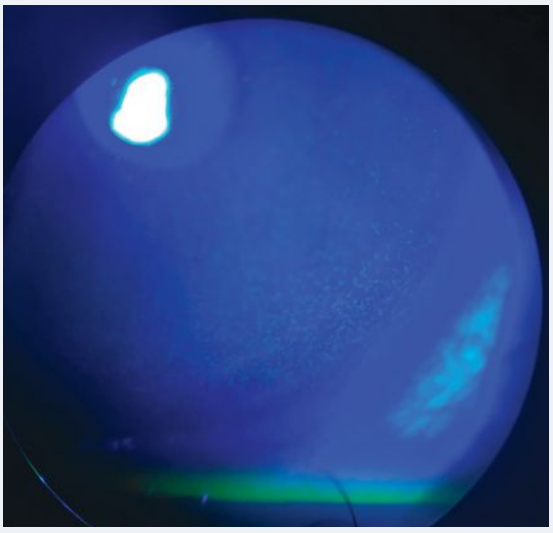

Fig. 4. Superficial punctate keratitis and dry eye syndrome in the left eye seen in a 62-year-old man with type 2 diabetes.

plantation to restore corneal integrity. Early detection of corneal complications can help prevent the need for these more aggressive treatments.

For neuropathic ocular pain, botulinum A toxin injections along the trigeminal nerve have relieved symptoms in some patients. In a study using botulinum A toxin for migraines, patients reported reduced ocular pain and photophobia in addition to relief of migraine symptoms. Injecting botulinum A toxin into the levator palpebrae superioris can serve as a temporary tarsorrhaphy for patients with severe signs, although it has visual and cosmetic implications.

Permanent tarsorrhaphy is rarely performed now due to the advancement of new treatment options for corneal disease. Corneal neurotization is reserved for severe cases of neurotrophic keratitis.[25] This involves surgical nerve grafting of healthy nerves to reinnervate the anesthetic cornea and has had significant success. Additionally, many new treatments, including topical naltrexone therapies and thymosine beta 4, are currently under investigation and hold promise for these advanced corneal conditions.

TAKEAWAYS

As we gain more insight into diabetic keratopathy, novel treatments addressing the underlying disease process can help many patients with this condition. Ongoing research is necessary to enhance our treatment of the various corneal complications associated with diabetes mellitus. In practice, the early recognition of signs and symptoms is crucial for the preservation of patients' vision and improving their quality of life.

Diabetic corneal complications initially present with subtle signs that can be easily overlooked, especially since diabetic eye examinations mainly focus on the posterior segment. Timely intervention can prevent severe corneal damage, such as ulceration and perforation, which require more severe therapy. Optometrists play a key role in managing patients with diabetes and ensuring their overall well-being and quality of life; thus, we must be equipped to recognize and address these complications when they arise. RCCL

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CORNEAL COMPLICATIONS OF DIABETES

CE TEST ~ NOVEMBER/DECEMBER 2024

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1. **Which layer of the cornea may be affected in diabetic patients?**
   a. Corneal epithelium.
   b. Corneal stroma.
   c. Corneal endothelium.
   d. All of the above.

2. **What role do insulin-like growth factor binding proteins play in diabetic corneal complications?**
   a. They increase insulin sensitivity.
   b. They compete with insulin-like growth factor, affecting wound healing.
   c. They improve corneal nerve regeneration.
   d. They stimulate tear production.

3. **What does polymegathism refer to in the context of corneal endothelial cells?**
   a. Decreased size of endothelial cells.
   b. Variation in the size of endothelial cells.
   c. Decreased density of endothelial cells.
   d. Increased thickness of the cornea.

4. **Which of the following tests is used to check corneal sensitivity in diabetic patients?**
   a. Schirmer's test.
   b. Pachymetry.
   c. Esthesiometry.
   d. Tear break-up time.

5. **Which stage of neurotrophic keratitis involves stromal melting and ulceration?**
   a. Stage 1.
   b. Stage 2.
   c. Stage 3.
   d. Stage 4.

6. **What condition is referred to as "pain without stain"?**
   a. Neurotrophic keratitis.
   b. Neuropathic pain.
   c. Superficial punctate keratitis.
   d. Recurrent corneal erosions.

7. **Which procedures should be considered with caution in uncontrolled diabetic patients?**
   a. Cataract surgery.
   b. LASIK.
   c. PRK.
   d. All of the above.

8. **Which recently approved FDA-approved treatment is designed to promote nerve regeneration in neurotrophic keratitis?**
   a. Cyclosporine.
   b. Artificial tears.
   c. Miebo (100% perfluorohexyloctane, Bausch + Lomb/Novaliq).
   d. Oxervate.

9. **Which test can be used to assess the degree of tear production in patients?**
   a. Noninvasive tear break up time.
   b. Schirmer's test.
   c. Meibography.
   d. Korb-Blackie Test.

10. **What is the function of matrix metalloproteinases in the tear film?**
    a. Promote collagen formation.
    b. Promote inflammation.
    c. Increase tear secretion.
    d. Stimulate mucin production.

11. **What are the potential complications for diabetic patients wearing contact lenses?**
    a. Reduced hydration and increased risk of infection.
    b. Increased oxygen exchange.
    c. Increased lipid deposits.
    d. Poor contact lens centration.

12. **What role does substance P play in the cornea of diabetic patients?**
    a. Stimulates tear production.
    b. Promotes epithelial healing.
    c. Causes corneal endothelial dysfunction.
    d. Delays wound healing.

13. **Which stage of neurotrophic keratitis is characterized by an oval persistent epithelial defect with rolled edges?**
    a. Stage 1.
    b. Stage 2.
    c. Stage 3.
    d. Stage 4.

14. **What condition is referred to as "stain without pain"?**
    a. Neurotrophic keratitis.
    b. Neuropathic pain.
    c. Superficial punctate keratitis.
    d. Recurrent corneal erosions.

15. **Which procedure involves surgical nerve grafting to reinnervate the corneal in severe neurotrophic keratitis?**
    a. Phototherapeutic kerectomy.
    b. Corneal transplantation.
    c. Tarsorrhaphy.
    d. Corneal neurotization.

16. **Which test should you consider in-office, if suspecting neuropathic pain?**
    a. Brightness acuity test.
    b. Pachymetry.
    c. Proparacaine test.
    d. Endothelial cell count.

17. **Which of the following treatments can be considered for corneal complications related to diabetes?**
    a. Oxervate.
    b. Amniotic membranes.
    c. Autologous serum.
    d. All of the above.

18. **Which stage of neurotrophic keratitis is characterized by punctate keratopathy?**
    a. Stage 1.
    b. Stage 2.
    c. Stage 3.
    d. Stage 4.

19. **Which medications have been used in patients with neuropathic pain?**
    a. Gabapentin.
    b. SSRIs.
    c. Pregabalin.
    d. All of the above.

20. **Which factor plays a role in the corneal complications seen in diabetics?**
    a. Vascular endothelial growth factor.
    b. Advanced glycation end products.
    c. Low-density lipoproteins.
    d. Angiotensin converting enzyme.

Examination Answer Sheet

Corneal Complications of Diabetes: What ODs Need to Know

Valid for credit through November 15, 2027

Online: You can take this exam online at www.revieweducationgroup.com. Upon passing the exam, you can view the results immediately and download a real-time CE certificate. You can view your test history any time on the website.

Directions: Select one answer for each question in the exam and completely darken the appropriate circle. A minimum score of 70% is required to earn credit.

Mail to: Jobson Healthcare Information, LLC/WebMD, 283-299 Market Street, 2 Gateway Center, 4th Floor, Newark, NJ 07102.
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Credit: This course is COPE-approved for two hours of CE credit. Course ID 94480-SD.

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Salus University has sponsored the review and approval of this activity.

Processing: There is a four-week processing time for this exam.

Answers to CE exam:

1.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
2.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
3.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
4.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
5.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
6.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
7.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
8.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
9.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
10.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
11.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
12.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
13.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
14.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
15.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
16.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
17.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
18.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
19.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
20.	Ⓐ	Ⓑ	Ⓒ	Ⓓ

Post-activity evaluation questions:

Rate how well the activity supported your achievement of these learning objectives:
1=Poor, 2=Fair, 3=Neutral, 4=Good, 5=Excellent

21. Recognize the prevalence and impact of diabetes on eye health. ① ② ③ ④ ⑤
22. Identify anterior segment complications related to diabetes. ① ② ③ ④ ⑤
23. Assess corneal health and function among patients with diabetes. ① ② ③ ④ ⑤
24. Develop treatment and management plans for diabetic patients. ① ② ③ ④ ⑤

25. Based upon your participation in this activity, do you intend to change your practice behavior? (choose only one)

Ⓐ I do plan to implement changes in my practice based on the information presented.

Ⓑ My current practice has been reinforced by the information presented.

Ⓒ I need more information before I will change my practice.

26. Thinking about how your participation in this activity will influence your patient care, how many of your patients are likely to benefit? (please use a number): ☐

27. If you plan to change your practice behavior, what type of changes do you plan to implement? (check all that apply)

Ⓐ Apply latest guidelines Ⓑ Change in pharmaceutical therapy Ⓒ Choice of treatment/management approach
Ⓓ Change in current practice for referral Ⓔ Change in non-pharmaceutical therapy Ⓕ Change in differential diagnosis
Ⓖ Change in diagnostic testing Ⓗ Other, please specify: _____

28. How confident are you that you will be able to make your intended changes?

Ⓐ Very confident Ⓑ Somewhat confident Ⓒ Unsure Ⓓ Not confident

Ⓐ Formulary restrictions
Ⓑ Time constraints
Ⓒ System constraints
Ⓓ Insurance/financial issues
Ⓔ Lack of interprofessional team support
Ⓕ Treatment related adverse events
Ⓖ Patient adherence/compliance
Ⓗ Other, please specify: _____

29. Which of the following do you anticipate will be the primary barrier to implementing these changes?

30. Additional comments on this course: _____

Please retain a copy for your records. Please print clearly.

First Name _____
Last Name _____
E-Mail _____

The following is your: ☐ Home Address ☐ Business Address

Business Name _____
Address _____
City _____ State _____
ZIP _____
Telephone # ___ - ___ - ____
Fax # ___ - ___ - ____

Rate the quality of the material provided:
1=Strongly disagree, 2=Somewhat disagree, 3=Neutral, 4=Somewhat agree, 5=Strongly agree

31. The content was evidence-based. ① ② ③ ④ ⑤
32. The content was balanced and free of bias. ① ② ③ ④ ⑤
33. The presentation was clear and effective. ① ② ③ ④ ⑤

By submitting this answer sheet, I certify that I have read the lesson in its entirety and completed the self-assessment exam personally based on the material presented. I have not obtained the answers to this exam by any fraudulent or improper means.

Signature _____ Date _____

Lesson 125483, RO-RCCL-1124

Progress with the KPro

Choosing an ideal contact lens for patients with this device can be overwhelming. Here is a breakdown of options and considerations.

In our last column, we left off with our patient being diagnosed with an advanced *Pseudomonas* infection, prompting the implantation of a Boston KPro Type 1. The use of the Boston KPro is rare and reserved for when a corneal transplant has a guarded prognosis or when all other options have failed.

The major components of the KPro device include a front plate composed of polymethylmethacrylate (PMMA), a donor corneal graft button and a back plate composed of PMMA or titanium.[1] The corneal tissue health is of significant concern, as it is particularly vulnerable to evaporative dry eye complications, among many others.[1] These complications include epithelial dysfunction, stromal thinning, corneal melt, dellen formation, perforation, aqueous leakage and infection.[1] When the KPro was originally introduced, the conjunctival flaps were used to protect this vital donor tissue.[1] Although still used, conjunctival flaps have largely been replaced with long-term bandage contact lens wear due to conjunctival retraction.[1]

BANDAGE CONTACT LENSES

This tool has long-established therapeutic benefits in wound healing, pain management and ocular surface protection. First approved for therapeutic usage in the 1970s, indications for bandage contact lenses have blossomed over time to include, but are not limited to, corneal abrasion, corneal erosion, dry eye, graft-vs.-host disease, post-procedurally including the KPro and more.[2,3] As of the writing of this article, there are currently three FDA-approved silicone hydrogel lens materials approved for bandage contact lens usage: balafilcon A, lotrafilcon A and senofilcon A.[3] The higher oxygen transmissibility of silicone hydrogels has been of particular benefit in diseased ocular surfaces, resulting in reduced corneal edema and hypoxia-related complications with extended-wear contact lens use.[3]

When managing your KPro patients, a proper bandage contact lens fitting is essential to maintain corneal tissue health and longevity.[4] Before surgery is performed, patients are informed and educated on proper contact lens wear. Patients must understand they will need lifelong bandage lens wear with prophylactic antibiotic treatment to help prevent infection and various other complications for which they are at higher risk.[4] Lenses are placed on the ocular surface by the surgeon following surgery completion. Most providers recommend removal and replacement every one to three months, which should only be performed by the physician, due to the relatively fragile nature of the donor tissue.[4]

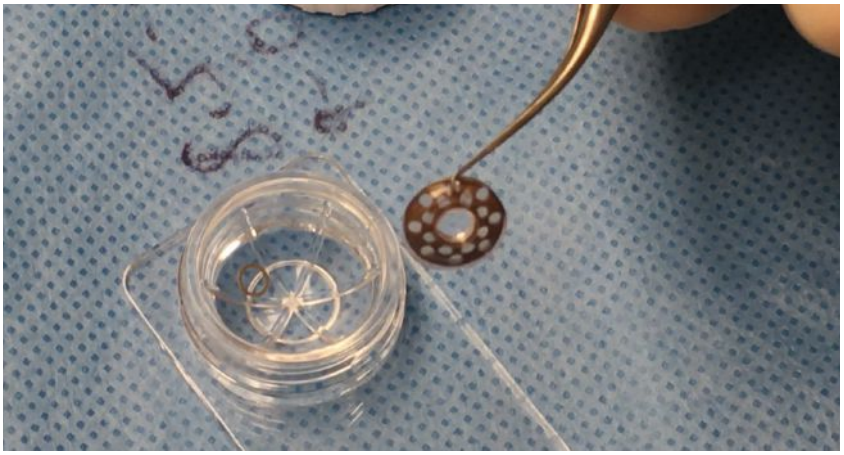
CONTACT LENSES FOR KPROs

The most commonly used bandage contact lens for KPro patients is the Kontur soft lens (Kontur Kontact Lenses). Kontur contact lenses are comprised of 55% water, use methafilcon A hydrogel material and have an oxygen permeability (Dk) of 18.8. They are available in a wide variety of parameters, with base curve options ranging from 6.8mm to 9.8mm and available diameters ranging from 12mm to 24mm, allowing the practitioner ample options to achieve a successful lens fitting. Powers range from +10.00D to -20.00D with astigmatic powers of -0.75D to -5.00D in all axis locations. This broad range allows the patient the ability to achieve their best possible vision. After the completion of surgery, a plano Kontur lens with a 16mm diameter and 9.8 base curve, which is provided by the manufacturer, is placed on the eye.

The extended-wear nature of lenses in KPro patients presents with its own difficulties. Although methafilcon A has a Dk of 18.8, the low oxygen transmissibility is not of significant concern, due to the donor tissue being considered a carrier.[4] Even though methafilcon A is considered a group IV hydrogel material (water content greater than 50% and ionic material), it is particularly good at resisting external lipid and protein deposition, which is important for lens comfort and vision in extended-wear KPro patients.[4,5] Group IV hydrogel materials typically accumulate deposits deep within the material matrix instead of the lens surface and plateaus in total deposition after one to seven days of wear.[5] Compare this to group II hydrogel lenses (water content greater than 50% and non-ionic material), which cumulatively deposits on the lens surface without plateauing.[5]

Other soft contact lenses have been used successfully with KPros as well. Custom soft lenses dominate the literature, with Alden Optical and X-Cel Specialty Contacts being preferred.[4] Some popular options are the HP 49 (hioxifilicon B, 49% water, Dk 15) from Alden Optical and X-Cel Specialty Contacts' multiple Flexlens designs (atypical refractive correction, spherical, tri-curve keratoconus and post-refractive lenses, 49% water and large diameter) available in many material options (polymacon, 38% water;

Photo: Brandon Ayres, MD



A bandage contact lens or other lens type, like sclerals, must be used to protect the donor tissue.

hefilcon A, 45% water; hioxifilicon B, 49% water; methafilcon A, 55% water; acofilcon A, 58% water; hioxifilcon A, 59% water; efrofilcon A, 74% water).[4]

FDA-approved soft bandage contact lenses have been used with KPros, too.[4] However, case reports have shown that these lenses require more lens trials to achieve an acceptable fit in KPro patients, and in some cases, were unable to reach an acceptable fit.[4] The lack of available lens options (*i.e.,* base curve and diameter) make the larger soft lenses preferable. Even though silicone hydrogels allow for greater oxygen transmissibility to the donor tissue, they are prone to increased lens deposits and discomfort.[5]

If an adequate fit with soft lenses cannot be achieved for reasons such as poor comfort and vision, scleral and hybrid lenses have been shown to be an additional option. Scleral lenses provide support for the ocular surface by providing a reservoir of sterile saline that bathes the eye throughout the day. Special considerations need to be taken into account with sclerals when glaucoma drainage devices are involved, though, as glaucoma is highly common in KPro patients. There is no established wear schedule with scleral lenses, with the following guides being used currently: a 12/12 schedule with around the clock wear but switched with a second set every 12 hours; wear during awake hours and soft lens nightly wear while sleeping; continuous 24-hour wear; and wear while awake.[6]

While hybrid lenses are mentioned in the literature as an option for KPro patients, there is minimal information about fitting them.[4] Use your trial set to get the hybrid lens to stabilize, then modify from there. The lenses need to be exchanged around every three months, depending on the patient. Keep in mind that this may not be the most cost-effective option for your patient.[4]

As with all lens-wearing patients, a proper contact lens fit is paramount—especially with KPro patients. A proper fit will show good coverage of the tissue with acceptable movement. Additionally, the lens should be large enough to provide centration.[4] As a similar consideration like with scleral lenses, the diameter of the soft lens needs to account for the likely presence of glaucoma drainage devices; this is because erosion has been shown to occur at the edge of the lens.[4] Large conjunctival elevations may also allow for pockets of air to develop under the contact; this could lead to focal drying. A properly fit lens should show no edge fluting (flat fit), air bubbles (steep fit) or vascular attention (tight fit).[4]

A lens that fits poorly over the eye can subsequently lead to infection. It is also documented that patients with the Boston KPro are prone to contracting infections, and this is why this patient subset is put on lifelong prophylactic antibiotics. The use of a contact lens increases the risk of infections, and a poorly fit contact lens will raise the chances of infection and complications. Our next column will address the most common complications of the Boston KPro. RCCL

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Surface Tension

Conjunctival cysts may cause worries over potential malignancy, but they're often benign.

An 84-year-old man presented for evaluation of conjunctival lesion OS with concerns for potential malignancy. The patient reported the lesion "had been there for years," and he denied discomfort. The patient was diagnosed with a large multi-lobular conjunctival cyst and monitored yearly.

Conjunctival cysts are benign fluid-filled sacs. They vary in size and may be asymptomatic or cause symptoms such as discomfort, irritation or foreign body sensation. The pathogenesis is multifactorial, involving mechanical, developmental and inflammatory processes that disrupt the normal cellular architecture of the conjunctiva.

One of the most common mechanisms is blockage of the superficial or deep lymphatic drainage system, leading to fluid accumulation within the cyst, which is typically thin and clear. The pressure within the cyst can eventually cause it to become more prominent, leading to noticeable swelling or bulging on the conjunctiva.

Another important pathway involves the entrapment and proliferation of epithelial cells. A cyst forms as squamous epithelial cells lining the conjunctiva undergo excessive proliferation and eventually form a sac-like structure. Over time, these cells secrete fluid, causing the cyst to enlarge. The cystic structure filled is with cellular debris, tears and sometimes inflammatory exudates. This may be congenital but often happen after trauma or surgical procedures, such as cataract surgery.

Inflammation and infection can also contribute to development of conjunctival cysts. Bacterial or viral conjunctivitis, blepharitis or chronic dry eye disease can lead to localized inflammatory responses that may impair normal glandular function or damage the conjunctival epithelium and lead to the formation of cysts.

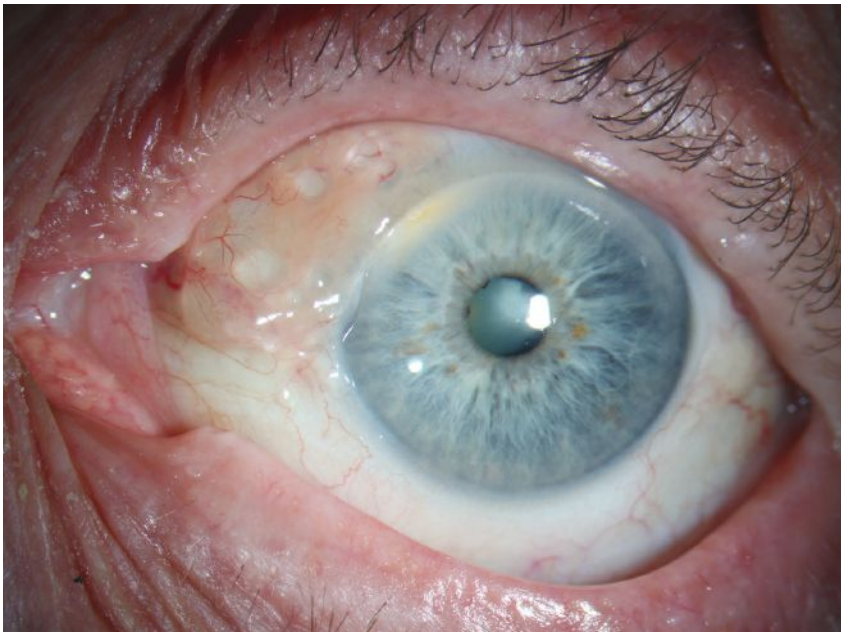
In some cases, conjunctival cysts can be congenital. These typically form during fetal development, when epithelial remnants from the embryonic stage fail to undergo proper regression or differentiation. As a result, epithelial-lined cysts are left behind within the conjunctiva.

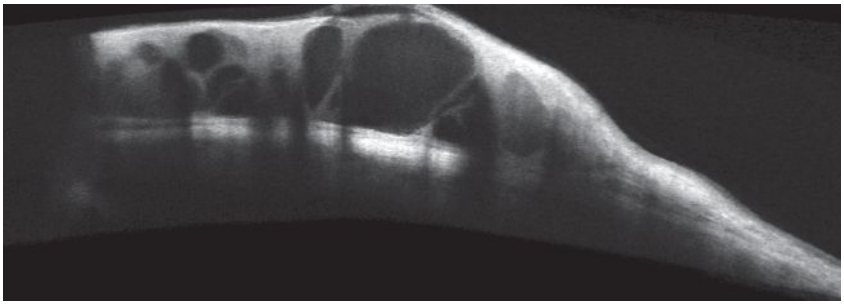
Other potential contributing factors include age-related changes in the conjunctiva, mechanical trauma and autoimmune disorders. These conditions can alter the normal drainage and function of the conjunctival structures, leading to cyst formation.

Treatment, when needed, often involves aspiration or surgical removal, usually with a low risk of recurrence.

It is always wise to differentiate a cyst from a more malicious lesion such as conjunctival neoplasm. While cysts are smooth, round and fluid-filled, neoplasms are solid and irregular with variable pigmentation.

OCT imaging of our patient showed superficial fluid-filled vacuoles, which remained stable over time. Since he was comfortable, no treatment was indicated. RCCL





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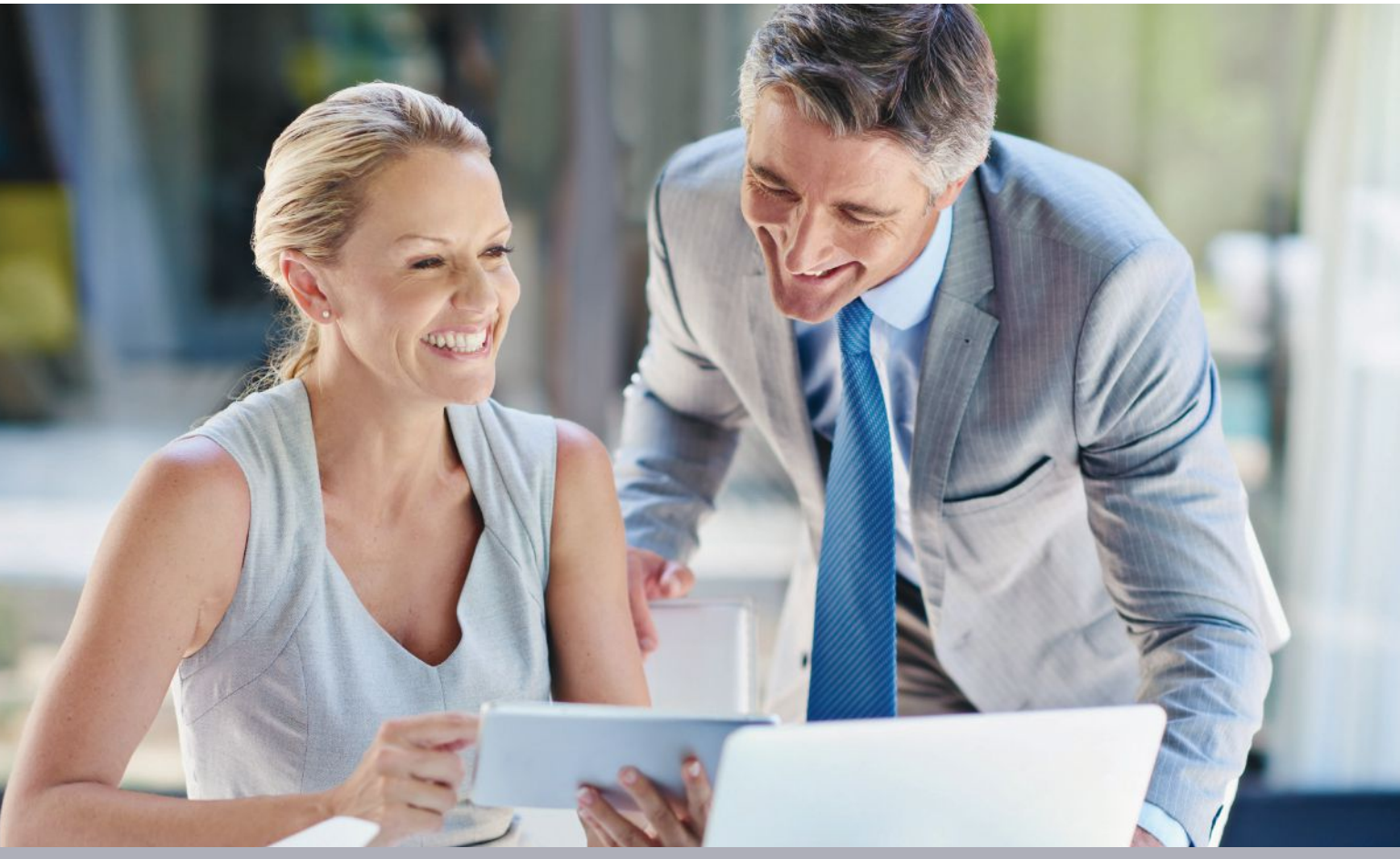

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