

# The Need for Therapies to Address Postoperative Corneal Edema

Cataracts affect nearly 25 million Americans age 40 and older, and by the age of 75, nearly half of all Americans have cataracts.<sup>1</sup> Advances in cataract surgery over time have led to it being an overwhelmingly successful surgery with minimal adverse events. This had led to incredibly high expectations from patients. However, there remain certain patients that emerge from cataract surgery with persistent corneal edema that is troublesome for both patients and surgeons. In many cases, the surgeon is aware that the cornea is not healthy going into surgery, or that the surgery was complex enough to cause increased trauma. Recently, Michael Greenwood, MD; Jai Parekh, MD, MBA, FAAO; Arsham Sheybani, MD; Robert Weinstock, MD; and Dagny Zhu, MD, discussed patients with an exceptional response to phacoemulsification, as well as the gap in tools to care for them.



BY MICHAEL GREENWOOD, MD;  
JAI PAREKH, MD, MBA, FAAO; ARSHAM SHEYBANI, MD;  
ROBERT WEINSTOCK, MD; AND DAGNY ZHU, MD

## How do you identify situations in which the cornea is not likely to heal well following cataract surgery? What are the risk factors prior to surgery?

**Dr. Weinstock:** While cataract surgery replaces a cloudy lens with a pristine, new lens, the cornea must also be healthy and clear for a patient to see well. There are several conditions where the baseline cornea is unhealthy, Fuchs' Corneal Dystrophy being one of the most well-known. If the corneal lining is hazy or patients have less than 2,000 corneal endothelial cells, the trauma of cataract surgery can damage those cells enough that they never fully recover. There are multiple factors, but the result is a large subset of patients that run a high risk for corneal edema after cataract surgery.

**Dr. Sheybani:** There are many situations where we are starting cataract surgery at a disadvantage in terms of corneal endothelial cells. My colleagues and I published a review paper showing that patients with

pseudoexfoliation syndrome and pseudoexfoliative glaucoma have lower endothelial cell density than control patients.<sup>2</sup> Anytime I'm using an AC IOL, a scleral fixated IOL, or a sutured IOL, these are generally cases where the surgery itself is complicated, so the case is taking longer, you're irrigating more, and you may be doing a vitrectomy. As you have general attrition of cornea cells, it's no surprise that down the line you may have corneal damage that requires a transplantation.

**Dr. Zhu:** I have a lot of patients with very advanced cataract disease. By the time I am seeing them, they have lost a good amount of vision, and their cataracts are rock-hard and solid. That makes them very difficult to remove with phacoemulsification. The greatest risk is when these patients also have a shallow anterior chamber. This creates a very high risk of the phacoemulsification and ultrasound energy causing long-term damage to the corneal

cells. With these patients, I often see a significant amount of corneal swelling and opacity on the first day of surgery. Their vision is very poor, sometimes worse than prior to surgery. This obviously leads to a lot of uneasiness and unhappiness for the patient. They are not thrilled with their outcome or me as a surgeon, and I'm also worried about long-term corneal endothelial damage and not knowing if they will have a continued loss of endothelial cells that may require a corneal transplant in the future.

**Dr. Parekh:** This is a great time in eye health. We really have very good outcomes with cataract surgery. However, we have not been able to improve the quality of patients that come to see us. I still have over 50% of patients that come to me over the age of 65, and we know that increased age and increased cataract density negatively impact endothelial cell loss following even routine cataract surgery.<sup>3</sup>

**Dr. Greenwood:** Whenever we perform cataract surgery, we know we are causing endothelial cell loss in the range of 10%.<sup>4</sup> But in patients who already have a compromised endothelium, the resulting corneal edema can take a while to go away. If you talk to your patients ahead of time and tell them they have an endothelial problem, that they are going to take longer to heal after cataract surgery, and that they might need a corneal transplant, it can make them very hesitant to undergo surgery.

### What are the risk factors for persistent corneal edema that may arise during surgery?

**Dr. Weinstock:** During cataract surgery we are irrigating and adding fluid into the eye and then creating suction as we remove the cataract. The denser the cataract, the more ultrasonic energy must be applied to break it up, and that vibrational energy increases free radicals and causes damage to the endothelial cells. In cases of very dense cataracts, the removal of the cataract causes trauma that leads to corneal edema. A patient with a relatively healthy amount of corneal endothelial cells and a very dense cataract can end up with an indefinitely swollen cornea due to the prolonged surgical time, the high amount of fluid being pushed into the eye to break up the cataract, and the high levels of ultrasonic energy used. A patient with a dense cataract almost always has corneal edema post-surgery. Sometimes it is persistent corneal edema, and the patient ends up needing a corneal transplant. That is a really difficult discussion to have with patients.

**Dr. Sheybani:** Whenever you are operating in conditions that leave

you 'behind the eight ball' regarding the endothelial cells, it's important to protect them at the time of surgery. Situations in which the risk is higher include anterior chamber IOLs, a scleral fixated IOL, a sutured IOL, or an iris sutured IOL. All of these lenses have similar complication rates in terms of requiring additional operations, corneal transplantations, endothelial transplantation, bleeding, and other issues.

**Dr. Greenwood:** While Fuchs' Dystrophy is probably the biggest risk factor of prolonged corneal edema following cataract surgery, there are others that come into play. You may have a shallow chamber or a very brunescent cataract. Perhaps the patient has loose zonules, a dislocated IOL, a previous tube shunt, or a concomitant MIGS procedure. These are eyes that potentially will experience more trauma during the cataract procedure. For any patient where we are in the eye longer to get the cataract out, the viscoelastic goes away, and so the cornea is at more risk for damage. These patients would benefit from something that would help the cornea heal faster.

### What is the impact of persistent corneal edema and how is it currently managed?

**Dr. Weinstock:** When the corneal endothelial cell count is so low that the cornea has a hard time maintaining a hydration level necessary to keep it crystal-clear, the patient's vision is compromised. In extreme cases, when those cells are so few in number and so dysfunctional, we have to do a DMEK or DSEK to replace the endothelial lining. It's a fairly involved procedure to try and restore clarity to the cornea.

**Dr. Parekh:** All patients want immediate good visual outcomes, but those with compromised corneal endotheliums may not improve for up to several months. That creates concerned patients, and I have to reassure them while also keeping them on chronic steroids and Muro 128<sup>®</sup> ointment (Bausch + Lomb). Then I have to talk to them about possibly having a procedure that removes the diseased layer of the cornea, or perhaps a corneal transplant. I am a corneal surgeon and can perform these procedures, but many of my colleagues have to refer a patient out for these procedures. Even a patient with prolonged edema that resolves spontaneously causes you to delay surgery in the second eye, because chances are it will also require a prolonged postoperative recovery. It can be a very frustrating problem for patients and surgeons.

**Dr. Zhu:** I see patients with advanced corneal disease almost every day. It's always important for cataract surgeons to cause the least amount of damage and trauma possible so that patients heal rapidly and have healthy eyes long term. However, patients with diseased endothelial cells are already at risk, and an intervention like cataract surgery accelerates cell loss. Their corneal disease may not have been causing them noticeable problems prior to cataract surgery, so they blame the surgery. All I can do is take time to counsel the patient in advance so they are aware of the increased risk, inform them that they will not see well on the first day post-op, and explain that it may take several weeks for their vision to clear. If they have ongoing corneal edema beyond a month or two, that is highly correlated with needing a corneal transplant. If I sense that may

be the outcome prior to surgery, I may even offer them a corneal transplant at the same time as cataract surgery, as it is the only option to improve the endothelium.

### Is there a gap in care for addressing persistent corneal edema following complicated cataract surgery?

**Dr. Weinstock:** Sodium Chloride Hypertonicity Ophthalmic Ointment can be used to help reduce corneal edema, or sometimes we try lowering IOP in an effort to clear the cornea, but both of those have limited applications. It's very important for our industry to understand the impact of corneal cell health and the concept of protecting the corneal cells during cataract surgery. We understand that there is edema following cataract surgery which is generally transient; however, persistent edema is probably under reported. We'd love to have a tool to maintain the cellular health of the endothelium following surgery and throughout a patient's lifetime.

**Dr. Sheybani:** In my mind, there is a gap in patient care that would probably change outcomes, and this is an agent that protects the endothelium beyond the usual viscoelastics. This is particularly critical for comprehensive ophthalmologists in those rare cataract surgeries that have complications. I have patients who are referred for a dislocated lens or aphakia, and the first thing I do is get a functional measure of how their endothelium is working, because I want to counsel them on the risks of surgery. Unfortunately, some don't recover from their initial surgery, depending on how much we had to do in the eye, and that is frustrating for me personally. For those cases that

have a higher rate of corneal edema immediately post-op, it would be great if we had a way to treat the damaged endothelial cells rather than waiting to see if the edema resolves over time. We could potentially prevent corneal transplantations down the line.

Fuchs' patients, or patients needing certain kinds of trabecular meshwork stenting, could benefit from an agent that protects the endothelium. But I think the greatest need is for those cases that are just a bit more complicated.

**Dr. Zhu:** There are eyes with so many risk factors for corneal decompensation that using a femtosecond laser won't save them. I participated in a study that showed that in eyes with Fuchs' dystrophy, using a femtosecond laser did not decrease their risk of needing a corneal transplant down the road.<sup>5</sup> If a patient has corneal edema at 4 to 6 weeks, there is a very high chance they will need a transplant.

Viscoelastic is a kind of physical barrier intended to protect the corneal endothelium. Unfortunately, it gets sucked up throughout the cataract removal procedure, so it disappears almost as quickly as you put it in, particularly with dense cataracts. There is only so much we can do to physically shield the corneal endothelial cells. I do think there is a role for a product that can reduce oxidative stress and serve to rehabilitate or revitalize the cells so they could recover more quickly.

I think every patient should have the opportunity to receive a presbyopia-correcting lens, but there are many surgeons who shy away from advanced technology and stick with monofocal IOLs if they think there is a risk of endothelial compromise during

the cataract procedure. Patients need a healthy endothelium to enjoy the benefits of presbyopia-correcting IOLs. Even one month of corneal edema is a headache, particularly with these patients, and I would love an innovative technology that could speed up recovery and allow patients to see well as soon as possible. That is helpful to both the patients and the surgeon, especially in a practice like mine.

**Dr. Parekh:** We have done a very good job of talking about and maximizing ocular surface health once we had the tools to take care of it. We don't really have anything for endothelial disease in patients who are undergoing cataract surgery. Even though we are using more modern-day viscoelastics, and cataract surgical time has shortened significantly compared to 10 years ago, we have patients with low endothelial cell counts or other dystrophies who are going to get corneal edema. It would be great to have a tool to help mitigate the postoperative burden in these patients—one that would have them see better sooner and hopefully reduce the need for cornea transplants. In my practice, treating cataract patients with endothelial disease is a huge unmet need that is very frustrating.

Unmet needs aren't attractive because there is nothing to do for them. There's no doubt that eye care is an exciting specialty because there is so much innovation. But to date, there is no therapeutic to combat the level of endothelial disease we see in patients who are going to be undergoing cataract surgery. It's frustrating and challenging for all of us in cataract/anterior segment surgery. We've found ways to use certain

techniques intraoperatively to ‘be kinder to the corneal endothelium,’ but the course to visual recovery is still longer and more frustrating for both the patient and the surgeon.

### Are there any tools to protect the corneal endothelium on the horizon?

**Dr. Weinstock:** There has been some development in this space with the investigation of fibroblast growth factor (FGF) as a potential injectable solution at the time of cataract surgery to help the endothelial cells protect themselves against the trauma of surgery. FGF helps to metabolize free radicals faster, supporting the metabolism of those endothelial cells and ultimately giving the patient the best opportunity for the cornea to stay clear after surgery. This has the potential to help a lot of unhappy patients and prevent more invasive procedures down the road, such as DMEK, DSEK, or full corneal thickness transplant.

**Dr. Greenwood:** I recently participated in a clinical study of an investigative drug (TTHX1114), a novel engineered FGF1 compound that treats corneal diseases and disorders. We studied patients who underwent DSO, with or without cataract surgery. Some were given the investigative drug, and some were not. Not only did TTHX1114 decrease recovery time following DSO, we also saw that patients who received

the drug and underwent cataract surgery recovered just as quickly as patients who underwent DSO alone. This means that there is something going on with those endothelial cells that didn’t get removed that is helping the cornea clear faster and improve outcomes. To be able to provide this opportunity to patients so they don’t have to rely on a transplant is remarkable.

**Dr. Weinstock:** All cataract surgeons would welcome a therapy that allows us to maintain corneal clarity after cataract surgery, prevent the need for further treatments or surgeries, and help our patients see better. ■

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### MICHAEL D. GREENWOOD, MD

- Glaucoma, cornea, cataract, and refractive surgery, Vance Thompson Vision, Fargo, North Dakota
- [michael.greenwood@vancethompsonvision.com](mailto:michael.greenwood@vancethompsonvision.com);
- Twitter @migreenw
- Financial disclosure: Consultant to Trefoil

### JAI G. PAREKH, MD, MBA, FFAO

- CEO & Co-Founder/President of EyeCare Consultants of NJ, Woodland Park, New Jersey; Founder, Center for Ocular Surface Excellence-ECCNJ; Founder, BeSiTe Ventures & Impact; Clinical Associate Professor of Ophthalmology/The NY Eye & Ear Infirmary of the Icahn School of Medicine at Mt. Sinai, New York; Chief-Anterior Segment Ophthalmology & Head of The Research Institute, St. Joseph’s Health, New Jersey
- [kerajai@gmail.com](mailto:kerajai@gmail.com)
- Financial disclosure: Consultant to Trefoil

### ARSHAM SHEYBANI, MD

- Associate Professor, Ophthalmology and Visual Sciences, Washington University School of Medicine, St. Louis
- [sheybaniar@wustl.edu](mailto:sheybaniar@wustl.edu)
- Financial disclosure: Consultant (AbbVie/Allergan, Alcon, Nova Eye, Glaukos)

### ROBERT J. WEINSTOCK, MD

- The Eye Institute of West Florida, Clearwater, Hyde Park, Largo, St. Petersburg, and Westchase.
- [rjweinstock@yahoo.com](mailto:rjweinstock@yahoo.com)
- Financial disclosure: Consultant to Trefoil

### DAGNY C. ZHU, MD

- Cornea, cataract, and refractive surgeon; Medical Director; and Partner, NVISION Eye Centers, Rowland Heights, California
- [dagny.zhu@nvisioncenters.com](mailto:dagny.zhu@nvisioncenters.com);
- [www.dzeyemd.com](http://www.dzeyemd.com); Instagram and Twitter @dzeyemd
- Financial disclosure: Consultant to Trefoil