The Effects of Glaucoma and Glaucoma Therapies on Corneal Endothelial Cell Density

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Abstract: A healthy corneal endothelium is required for corneal clarity. Both the glaucoma disease state and its various forms of treatment can have adverse effects on the corneal endothelium. Both the presence of glaucoma and the magnitude of intraocular pressure elevation are related to endothelial cell loss (ECL). Topical medical therapy, laser glaucoma surgery, and intraocular pressure, glaucoma therapy, lasers, glaucoma decompensation.

Key Words: glaucoma, corneal endothelial cells, endothelial cell loss, intraocular pressure, glaucoma therapy, lasers, glaucoma surgery

ANATOMY AND PHYSIOLOGY

The corneal endothelium consists of a single layer of flattened cells, derived from the neural crest, that line the posterior surface of the cornea.1 These cells are anchored to the Descemet membrane, a collagen-based basement membrane secreted by the endothelium.1 They are highly metabolically active and thus mitochondria-rich. The dual functions of endothelial cells are essentially paradoxical: this layer of cells must remain permeable to nutrients and waste products delivered to and from keratocytes that lack a vascular bed to perform these functions, while simultaneously maintaining optimal corneal hydration (at 78%2) to ensure optical clarity.1 The former function is mediated by an incomplete zonula occludens between cells, permitting the passage of glucose and other molecules, while the latter function is maintained by an active pump system (mediated in part by the enzyme carbonic anhydrase) that moves water and ions from the stroma to the anterior chamber; this disparate combination of active and passive transport has been referred to as a pump-leak mechanism.3

NATURAL HISTORY OF ENDOTHELIAL CELL DENSITY (ECD)

Corneal endothelial cells (CECs) do not divide naturally, so the number present at the peak of embryological development—∼300,000 by the second trimester of gestation—represents the lifetime maximum cell population.4 This corresponds to an ECD of 5000 to 6000 cells/mm² in the fetal eye,

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decreasing to ∼2500 to 3000 cells/mm² in early adulthood. This decrease in the first 2 decades of life is attributable to ocular growth and an increase in the posterior corneal surface area rather than CEC demise. From ages 15 to 85 years, the attrition rate is 0.6%/year and does not accelerate with age.

ECD IN EYES WITH GLAUCOMA

Primary open-angle glaucoma (POAG) is associated with reduced ECD. In a case-control study in Chinese eyes that included 60 healthy eyes and 60 eyes with POAG, the mean ECD was significantly greater in healthy eyes than in POAG eyes \( (P < 0.001) \). In a study of similar design conducted in Korean eyes, POAG but not normal-tension glaucoma was associated with a lower ECD compared with healthy eyes. This finding—significantly lower ECD in eyes with POAG compared with healthy eyes—has been confirmed in studies conducted in Germany and Canada.

Elevated intraocular pressure (IOP) is associated with endothelial cell loss (ECL), as evidenced by greater ECL seen in eyes with POAG than with normal-tension glaucoma. Eyes with glaucoma types characterized by marked IOP elevations—specifically angle-closure and pseudoexfoliation glaucoma—are also prone to ECL. Angle-closure glaucoma is associated with significant \( E_{CD} \), with the degree of ECL correlated with the duration of IOP elevation. Eyes with pseudoexfoliation syndrome (no glaucoma) have lower ECD than unaffected control eyes. Eyes with pseudoexfoliation glaucoma have significantly lower ECD than healthy eyes, and normotensive unaffected fellow eyes. In both angle-closure glaucoma and pseudoexfoliation glaucoma, however, pathophysiologic factors intrinsic to these types of glaucoma other than IOP may also be contributory to ECL. Eyes with pigment dispersion syndrome with or without glaucoma have ECD similar to healthy controls. The relationship between glaucoma and ECD is particularly important in patients with already-compromised corneas, as glaucoma is a key risk factor for graft failure after penetrating or lamellar corneal transplantation.

ECD AND GLAUCOMA THERAPIES

The approach to glaucoma therapy is to lower IOP with the goal of preventing or delaying disease progression and the development of visual dysfunction. IOP reductions can be achieved with medical therapy, with various laser procedures, or with incisional surgery.

Separating the effects of glaucoma and its treatment on ECD can be challenging, as many studies of ECD in glaucomatous eyes were conducted in eyes receiving some form of glaucoma therapy. A small study of 62 eyes demonstrated lower ECD in medically treated versus untreated eyes with glaucoma. Multiple other studies have found no differences in ECD between untreated glaucoma patients and healthy controls; between healthy controls, untreated ocular hypertension (OHTN), medically treated OHTN, and medically treated POAG patients; and between treated and untreated POAG patients. An eye bank study of over 19,000 eyes found no differences in ECD among eyes that were or were not treated with IOP-lowering medications; ECD was also independent of the drug class and number of IOP-lowering medications used. The Ocular Hypertension Treatment Study randomized >1600 eyes with OHTN to medical treatment or observation; after 78 to 108 months of treatment, no changes in ECD or cellular morphology (coefficient of variation and the percent hexagonal cells) were seen between groups.

The known effects of each glaucoma treatment modality are reviewed below.

Medications

Medical therapy for glaucoma is typically applied via topical ophthalmic administration. Therapy is daily—often multiple times per day—and is chronic, often persisting through patients’ remaining lifetimes. Formulations of topical medications include both active drug components and various excipient ingredients that serve as buffers, pH regulators, solubility enhancers, and preservatives. Discerning potential effects of each component versus the mixture as a whole is not possible in clinical studies. Each drug class is discussed below.

Prostaglandin Analogs

These drugs are analogs of prostaglandin \( F_{2α} \) and their effects on IOP are mediated by an agonistic interaction with the \( F_{2α} \) receptor. In vitro, prostaglandin \( F_{2α} \) in concentrations lower than in commercial IOP-lowering prostaglandin analog formulations stimulates proliferation of bovine CECs, with a 2-fold increase in cell number in culture after 5 days of exposure. In a 12-month double-masked randomized trial designed to evaluate the effects of latanoprost, timolol, and the fixed combination of these 2 drugs on CECs in 369 subjects with OHTN or POAG, mean ECD in the latanoprost group increased by an insignificant 0.3% and in the fixed combination group by 0.1% after 12 months of therapy. A post hoc analysis of data from a phase 3 trial comparing the IOP-lowering effects of latanoprost and netarsudil alone and in fixed combination likewise revealed no significant changes in ECD in the latanoprost and latanoprost/netarsudil fixed combination groups after 90 days of daily exposure. In a masked cohort study, 12 months of therapy with preservative-free tafluprost significantly increased ECD \( (P = 0.0006) \) in eyes with OHTN or glaucoma. In a longer masked cohort study of 93 patients treated for 3 years with bimatoprost, travoprost, or preservative-free tafluprost, mean ECD decreased significantly in the tafluprost-treated eyes and increased significantly in bimatoprost-treated and travoprost-treated eyes; in this study, the most significant ECD changes occurred after month 24.

Beta-blockers (BBs)

Topical adrenergic antagonists (BBs) were first used for IOP reduction in 1977 and remained the preferred first-line therapy for 2 decades. Numerous nonselective \( β_1/β_2 \) and one relatively \( β_1 \) cardioselective BB have been commercialized. Timolol, the prototype nonselective BB, has no effect on ECD or CEC morphology with short-term (4 d) or 2 wk exposure in healthy subjects. A comparison of ECD between fellow eyes following 5 years of unilateral timolol therapy revealed no differences. A randomized clinical trial comparing the effects of latanoprost and timolol alone and in fixed combination found a 0.0% change in ECD following 12 months of daily timolol therapy. In another randomized trial, 12 months of exposure to timolol or betaxolol (a \( β_1 \) cardioselective BB), mean ECL was similar between the 2 groups (4.5% vs. 4.2%, respectively). The nonselective BB levobunolol also had no effect on ECD after 4 months of therapy in 10 patients with OHTN.

Carbonic Anhydrase Inhibitors (CAIs)

Carbonic anhydrase is an enzyme that plays a critical role in the CEC’s task of regulating corneal stromal hydration. Within the ciliary epithelium, inhibition of carbonic anhydrase
effectively lowers aqueous humor production and subsequently lowers IOP. CAIs for IOP reduction are available for both oral and topical ophthalmic dosing. No clinical data on the effects of oral acetazolamide or methazolamide on ECD were identified in the English-language PubMed-indexed literature. Two 3-month studies of topical dorzolamide therapy, dosed 2 or 3 times daily, demonstrated no changes in ECD or CEC morphology. A prospective randomized trial compared the effects of dorzolamide, timolol, and betaxolol on ECL; at 12 months, ECL in eyes treated with dorzolamide 3 times daily was 3.6%, which was similar to ECL in the BB-treated eyes (4.5% and 4.2%, respectively). A 12-month study of patients with OHTN or POAG treated with latanoprost with or without brinzolamide found no changes in ECD or CEC morphology in either group.

### Alpha-adrenergic Agonists

The chronic use of topical epinephrine—now a drug of historical use only—was associated with greater ECL in treated eyes with OHTN than in untreated fellow eyes; interestingly, the degree of IOP reduction was correlated with ECL in that eyes with greater IOP reductions also manifested greater ECL. No clinical data on the effects of other alpha-adrenergic agonist drugs—including dipivefrin, apraclonidine, and brimonidine—were identified in the English-language PubMed-indexed literature.

### Miotics

Both direct-acting and indirect-acting cholinergic agents have been used for IOP reduction in eyes with OHTN and glaucoma, although they are largely of historical value today with the exception of pilocarpine which still has value, particularly in pseudophakic and aphakic eyes. A study of long-term (range: 18 to 78 mo) use of pilocarpine gel 4% revealed no abnormal ECD values that could not be explained by comorbid ocular pathology. The ECL seen with the use of acetylcholine or carbachol for intraocular miosis during extracapsular cataract surgery was similar between the 2 drugs and consistent with expected ECL associated with extracapsular cataract surgery alone.

### Rho Kinase Inhibitors

In animal and nonglaucoma clinical studies, the use of rho kinase inhibitors promote CEC health, enhance endothelial cell wound healing, increase ECD in animal models, and enhance the resolution of corneal edema in humans with Fuchs’ dystrophy. A single drop of ripasudil in the eyes of 32 healthy volunteers produced decreases in ECD and percent hexagonal cells and increases in coefficient of variation within 15 minutes, all of which returned to pretreatment levels by 6 hours postdose. Short-term (1 wk) topical exposure to ripasudil dose twice daily had no effect on ECD in healthy volunteers. In phase 3 randomized clinical trial in eyes with open-angle glaucoma or OHTN, netarsudil alone or in combination with latanoprost had no effect of ECD following 3 months of therapy. Reversible morphological changes to CECs—including irregularly shaped cells with indistinct intercellular borders—have been reported in 1 patient using the fixed combination of netarsudil and latanoprost.

### Nitric Oxide (NO)

NO is known to promote the relaxation of vascular and trabecular endothelial cells. A NO-donating formulation of latanoprost has been developed and other NO-donating drugs in development include formulations of bimatoprost and CAIs. To date, no clinical data on the effects of NO or NO-donating compounds on ECD were identified in the English-language PubMed-indexed literature.

### Multiple Drug Regimens

Combinations of IOP-lowering therapies may have different effects on ECL than drugs used as monotherapy. This could arise due to the interaction between drugs or to cumulative effects of excipient ingredients, such as preservatives. For instance, the ubiquitous preservative benzalkonium chloride (BAK) has been implicated in ECL. In in vitro studies, ECL is greater after exposure to BAK-preserved formulations than to BAK-free formulations, and inadvertent use of preserved balanced salt solution or ophthalmic visscosurgical device during intraocular surgery can produce dramatic ECL. However, there are little clinical data to suggest the detrimental effects of multitherapies on CEC health. Fixed or unfixed combinations of latanoprost with timolol, brinzolamide, or netarsudil have been reported to cause no significant changes in ECD or CEC morphology. Also, the aforementioned eye bank study of >19,000 eyes found no dose-response relationship between the number of IOP-lowering medications and ECD.

### Summary

In summary, there is no evidence that any class or combination of topical IOP-lowering medications adversely affects ECD or CEC morphology.

### Laser Procedures

#### Iridotomy

In most studies, argon laser peripheral iridotomy (LPI) has been shown to have no effect on ECD or CEC morphology through up to 12 months of follow-up, and no correlation was seen between energy used and magnitude of ECL. In one study, ECL of 8% was reported 1 month after argon LPI. One study reported an increase in CEC size, proportional to the energy delivered, 3 months after argon LPI. A series of 6 eyes of 5 patients with generalized corneal decompensation averaging 3 years following argon LPI has been reported, only 2 of which had evidence of preexisting endotheliopathy (Fuchs’) at the time of corneal transplantation.

Studies of LPI performed with Nd:YAG laser are less consistent. Some studies reported no significant ECL through up to 6 months of follow-up after Nd:YAG LPI. Conversely, ECL of 7.4% has been reported as soon as 3 days posttreatment, rebounding to only 3.8% ECL by 3 months. Others have reported significant ECL following Nd:YAG LPI, some of which was reported as being focal to the iridotomy site. In eyes with chronic angle-closure glaucoma, ECD did not decrease more in eyes undergoing Nd:YAG LPI than in eyes not undergoing LPI after average follow-up of 3.2 years. A randomized fellow-eye comparison of argon and Nd:YAG LPIs in patients with bilateral primary chronic angle-closure glaucoma found 12-month ECL averaging 8% in argon-treated eyes versus 0% in Nd:YAG-treated eyes (P < 0.01). In angle-closure suspect eyes with anatomically narrow angles (ANA), there was no change in ECD or CEC morphology at 1 year after prophylactic LPI, and no difference in ECL over 3 years in eyes that did and did not undergo prophylactic LPI. A recent clinical trial demonstrated that primary cataract extraction was superior to primary LPI in controlling IOP in eyes with primary angle-closure glaucoma or...
primary angle closure with IOP > 30 mm Hg. The relative effects of these 2 treatments on ECD is unresolved. A randomized trial found no difference in ECL between eyes undergoing phacoemulsification or LPI after 6 months of follow-up, while a 2-year retrospective analysis reported significantly less ECL following phacoemulsification than combined argon-Nd:YAG LPI both 1 and 2 years after treatment. These disparate findings may be related to the duration of follow-up. In eyes with A&A that underwent combined argon and Nd:YAG LPI, the 1-year ECL was 1.7% with an additional 0.17% ongoing ECL through 7 years of follow-up. Overall, these studies generally support the conclusion that LPI performed with argon, Nd:YAG, or a combination of both, has modest effects on ECD over time.

**Trabeculoplasty**

Numerous studies have reported no effects of argon laser trabeculoplasty (ALT) on ECD through up to 12 months of follow-up. One study reported a significant increase in CEC size 6 months after ALT. Selective laser trabeculoplasty (SLT) has been reported to cause acute reductions in ECD during the first posttreatment week that rebound to pretreatment levels by 1 month. Other studies have found no changes in ECD or CEC morphology 1 hour to 6 weeks posttreatment.

A prospective analysis of eyes undergoing micropulse trabeculoplasty found no changes in ECD 6 months posttreatment.

Overall, these studies suggest that trabeculoplasty has no detrimental effect on ECD when performed on any laser platform.

**Summary**

LPI performed with either argon or Nd:YAG lasers appears to have only a modest and likely clinically insignificant effect on ECD in the majority of studies. Trabeculoplasty (ALT, SLT) has no overall effect on ECD.

**Surgical Procedures**

**Phacoemulsification**

Routine phacoemulsification in the general population has a well-described effect on ECD, with reductions occurring in the immediate postoperative period but stabilizing over time. The magnitude of ECL after elective phacoemulsification has been reported to be 7.6% to 9.5% within the first 2 weeks after surgery, 7.5% at postoperative day 30, 5% to 8% by 6 months, and ~7% by 6 to 12 months. The effect of phacoemulsification on ECD in glaucomatous eyes has also been characterized. In the control (phacoemulsification-only) group of the COMPASS and COMPASS XT supraciliary microstent study, the 3-month, 2-, 4-, and 5-year ECL was 10%, 9%, 7.5%, and 10.1%, respectively. In the pivotal trial of the second-generation trabecular microbypass device, ECL of 11.6% was seen by month 3 and 12.3% at month 24 in the phacoemulsification-only control group, confirming that ECL tends to occur within the first 3 months of surgery. A small single-surgeon comparison of eyes with (n = 19) and without (n = 25) POAG undergoing phacoemulsification demonstrated ECL at 6 months postoperatively of 9.1% in the nonglaucoma group and 17.2% in the eyes with concurrent POAG; this difference was not significant (P = 0.199), although the study may have been underpowered for this analysis.

Eyes with pseudoxefoliation may be at higher risk for ECL than eyes without. A series of eyes with pseudoxefoliation syndrome (no glaucoma) demonstrated ECL of 9.0% 3 months after phacoemulsification, while an age-matched control group of healthy eyes without pseudoxefoliation experienced only 3.4% ECL (P = 0.0216) in the same time frame. Conversely, a cross-sectional evaluation conducted 6 to 7 years after standalone phacoemulsification demonstrated comparable ECD in eyes with and without pseudoxefoliation syndrome, as well a comparable ECD in pseudoxefoliation syndrome and glaucoma.

Eyes with occludable angles may also be at increased risk for ECL after phacoemulsification, perhaps due to the shallower anterior chamber resulting in closer proximity of the phaco needle and the corneal endothelial surface. A prospective analysis of phacoemulsification in eyes with ANA demonstrated a significant change from baseline in ECD, with a 3-month ECL of 14.5% (P < 0.001). Shorter axial length, as well as steeper anterior corneal curvature, a greater degree of nuclear sclerosis, and higher IOP were all significant factors associated with ECL.

**Trabeculectomy**

Trabeculectomy without mitomycin C (MMC) is associated with ECL of 1.6% to 6.4% within the first 3 postoperative months. This is likely due to the statistically significant change from baseline in ECD, with a 3-month ECL of 14.5% (P < 0.001). Most of this likely occurs in the first few weeks postoperatively; a 3-month study found ECL of 4.6%, of which only 1.2% occurred between months 1 and 3. CEC morphology was unchanged at 3 months.

MMC appears to have an independent effect on ECD. While one study found no change in ECD or CEC morphology 3 weeks after trabeculectomy with MMC, other studies have found greater ECL in trabeculectomies augmented with MMC compared with unaugmented surgery. Within the first 3 postoperative months, trabeculectomy with MMC was associated with ECL of 8.7% to 14.5% compared with 3.7% to 4.6% ECL in trabeculectomy without MMC; these differences were statistically significant in both studies. As with unaugmented surgery, the ECL seen with MMC-augmented trabeculectomy appears to occur in the immediate postoperative period, with one study reporting 3- and 12-month ECL of 9.5% and 10.0%, respectively, indicating no significant ongoing ECL after the first few months. Focal ECL in the region of the bleb can be greater than the overall ECL. ECL at 24 months was greater in eyes with pseudoxefoliation glaucoma (18.2%) and uveitic glaucoma (20.6%) than in eyes with open-angle glaucoma (9.3%). In contrast, MMC use in nonpenetrating ocular surface procedures (eg, refractive surgery, pterygium excision) do not produce changes in ECD.

Bleb needling with MMC had no effect on ECD or CEC morphology through 12 months of follow-up. Postoperative subconjunctival injections of 5-fluorouracil, however, have been shown to reduce ECD. Direct eyelid application of MMC via sponges does result in intraocular ingress of MMC, with higher intraocular concentrations achieved with scleral compared with the episcleral application but no correlation with sponge size or exposure time. The magnitude of ECL is similar if MMC is applied before or after scleral flap dissection. This intraocular exposure and CEC damage can be mitigated by infiltrating the anterior chamber with an ophthalmic vicsurgical device before MMC application or by use of an anterior chamber maintainer during surgery.
Combined phacotrabeculectomy does not produce significantly greater ECL than either phacoemulsification alone \(^{120}\) or trabeculectomy alone. \(^{120,121}\) Two-site surgery is associated with greater ECL than 1-site surgery in eyes with average \(^{121,122}\) and short axial lengths. \(^{123}\)

Several studies have compared ECL in eyes undergoing trabeculectomy versus other procedures. Trabeculectomy is associated with greater ECL than nonpenetrating procedures such as deep sclerectomy (7.0% vs. 2.6%, respectively) at 12 months. \(^{124}\) Compared with trabeculectomy, Ahmed valve implantation is associated with similar ECL at 3 months (4.2% and 3.5%, respectively) \(^{125}\) and greater ECL at 6 months (1.9% vs. 9.4%) and 12 months (3.2% vs. 12.3%) postoperatively. \(^{126}\) In a randomized head-to-head comparison of trabeculectomy versus Ex-Press mini-shunt implantation, 24-month ECL was 2.2% and 18.0%, respectively, and while ECL stabilized by month 12 in the trabeculectomy group, ECL was ongoing through month 24 in the mini-shunt group. \(^{127}\) In another randomized trial, 12-month ECL was similar in trabeculectomy and mini-shunt eyes. \(^{128}\)

In a nonrandomized comparison, significant ECL was seen at 24 months after trabeculectomy but not mini-shunt implantation. \(^{129}\)

**Tube-shunt implantation**

ECL following Ahmed valve (New World Medical, Rancho Cucamonga, CA) implantation begins soon after implantation and continues over time. ECL of 0% to 5.8% has been reported at 1 month, \(^{125,130}\) 3.5% at 3 months, \(^{125}\) 7.9% to 11.5% at 6 months, \(^{130,131}\) 6.4% to 15.2% at 12 months, \(^{130,132,133}\) and 11.5% to 18.6% at 24 months. \(^{130,133,134}\) In a 24-month study, ECL at 1, 6, 12, 18, and 24 months was 5.8%, 11.5%, 15.3%, 16.6%, and 18.6%, respectively. \(^{130}\) In a study with an average follow-up of 43 months, incremental annualized ECL in years 1–3 were 10.7%, 7.0%, and 4.2%, respectively, with an ongoing average 2.7% annual decline thereafter. \(^{133}\)

Baerveldt tube-shunt (Johnson & Johnson, New Brunswick, NJ) implantation into the anterior chamber produces ECL of 7.2% at 6 months, \(^{135}\) 12.1% at 12 months, \(^{135}\) and 13.7% at 36 months. \(^{136}\) A recent 5-year study reported central and peripheral ECL of 36.8% and 50.1%, respectively. \(^{137}\) Implantation of the Baerveldt device into the vitreous cavity via a pars plana approach is associated with substantially less ECL. \(^{135,138,139}\) For both Ahmed and Baerveldt devices, the proximity of the tube tip to the corneal endothelium is directly proportional to ECL. \(^{138-140}\)

The Molteno valve produced comparable ECL to the Ahmed and Baerveldt devices in one study with a 24-month ECL of 12.4%. \(^{134}\) Conversely, a small study of 19 eyes found no significant changes in ECD through up to 26 months of follow-up after Molteno implantation. \(^{141}\)

The increase in ECL over time in eyes implanted with tube-shunts may be related in part to tube-cornea touch, which may be intermittent. This is somewhat common after tube-shunt implantation, especially in children, and can lead to mechanical trauma and loss of CECs. \(^{142,143}\)

**Novel Glaucoma Surgeries**

A number of novel IOP-lowering surgeries have been developed in recent years. Collectively these procedures seek a balanced efficacy/safety profile skewed more toward safety, with the goal of expanding surgical options in patients with moderate IOP reduction goals in whom the risks of traditional trabeculectomy or tube-shunt surgery may not be warranted. This loosely related family of procedures is often classified—based on the site of aqueous humor drainage—into the trabecular meshwork (TM), suprachoroidal, and subconjunctival procedures.

Procedures that facilitate aqueous humor drainage across the TM into Schlemm canal include excisional and incisional goniotomy procedures, ab interno trabeculotomy procedures, a trabecular microshunt, and a Schlemm canal microstent. In a prospective study, excisional goniotomy with the Kahook Dual Blade (New World Medical) combined with phacoemulsification was associated with ECL of 3.4% after an average 18 months postoperatively, with no relationship between degree of ECL and length of follow-up. \(^{144}\) In this study, fellow eyes underwent combined iStent-phacoemulsification, and ECL was greater in these eyes (9.0%) than in Kahook Dual Blade eyes (3.5%, \(P = 0.048\)) at 12 months. Incisional goniotomy with the Trabected (MicroSurgical Technology, Redmond, WA) produced no ECL at 6 months \(^{145}\) or 36 months, \(^{146}\) and incisional goniotomy with a microhook combined with phacoemulsification in Japanese eyes, ECL was 6% after a mean follow-up of 9.5 months. \(^{147}\)

Eyes receiving the first-generation iStent (Glaukos, San Clemente, CA) combined with phacoemulsification had a 12-month ECL of 13.2%, \(^{148}\) and Japanese eyes receiving 2 iStents as a standalone procedure had no measurable ECL at 6 months. \(^{149}\) In the pivotal trial of the second-generation iStent Inject (Glaukos), ECL at 24 months was 13.1% in the iStent-phacoemulsification group and 12.3% in the phacoemulsification-only group, most of which (12.5% and 11.6%, respectively) occurred in the first 3 months postoperatively; the proportion of eyes with ECL > 30% was also similar between groups (10.4% and 9.5%, respectively). \(^{149}\)

Eyes with POAG implanted with the Hydrus Schlemm canal microstent (Ivantis, Irvine, CA) at the time of phacoemulsification had a 6-month ECL of 11.7%, while ECL was 17.4% in 7.4% with POAG undergoing phacoemulsification alone in a prospective randomized trial. \(^{98}\) In a nonrandomized arm of the same study, eyes without glaucoma undergoing phacoemulsification alone had ECL of 9.1% at 6 months. \(^{148}\) ECD outcomes were not reported in the microstent’s international pivotal trial, \(^{150}\) but the Hydrus Instructions for Use document reports that 24-month ECL in the full international cohort was 14% in microstent-phacoemulsification eyes and 10% in phacoemulsification-only eyes at 24 months, with 13.6% and 7.2%, respectively, manifesting ECL ≥ 30% at month 24. \(^{151}\) An analysis of the subset of patients in that trial enrolled at sites in the United States (n = 331 eyes) was separately reported. \(^{152}\) In these eyes, the microstent-phacoemulsification group had 3- and 24-month ECL of 14.0% and 15.5%, respectively, while the corresponding ECL values in eyes undergoing phacoemulsification-only were 9.9% and 9.4%, respectively; the 3-month differences were not statistically significant, while the significance of the 24-month differences were not described. \(^{152}\)

The CyPass supraciliary microshunt (Alcon Laboratories, Fort Worth, TX) has been withdrawn from the global marketplace as a direct result of its adverse effect on ECD, a finding that manifested late in a safety extension of the device’s pivotal trial. \(^{153}\) Through 2 years postoperatively, ECL in the combined microstent-phacoemulsification and phacoemulsification-only groups was similar (12.0% vs. 8.7%, respectively). \(^{95}\) With longer follow-up in a safety extension study, eyes undergoing combined surgery with the microstent had ongoing ECL compared with the phacoemulsification-only group, with ECL of 18.4% and 7.5%, respectively, at 4 years and 20.4% versus 10.1%, respectively at 5 years. \(^{95}\) While there were no differences
between groups in terms of CEC morphology through 5 years of follow-up, the cumulative 5-year incidence of ECL > 30% was 27.2% in the microstent group and 10.0% in the phacoemulsification-only group. Device position was associated with ECL, with greater ECL in eyes with devices that protruded further into the anterior chamber and in closer proximity to the endothelium. The late manifestation of serious adverse events with this device has underscored the importance of long-term follow-up for novel procedures to fully characterize safety profiles.

The XEN gel stent (Allergan, Belfast, Ireland) shunts aqueous humor to the subconjunctival space. Similar 24-month ECL has been reported in eyes undergoing gel stent implantation as a standalone procedure (14.5%)4 and combined with phacoemulsification (14.3%).5 As with the supraciliary microstent, device positioning is crucial—the gel stent can migrate postoperatively with eye movements, touching the corneal endothelium and causing ECL.155 The Ex-Press mini-shunt (Alcon Laboratories) is a transcleral device that shunts aqueous humor into the subconjunctival space. A short-term study found no ECL in eyes receiving the mini-shunt at 1 and 3 months postoperatively.125 In other studies, ECL at 12 months was 10.0%158 and at 24 months was 18.0% in a randomized trial125 but insignificantly changed from baseline in a non-randomized prospective series.129 Device position is related to ECL; if implanted in the TM, 24-month ECL was reported to be 5.2%, but if implanted more anteriorly within the cornea, ECL of 15.1% was seen.157

Summary
Phacoemulsification results in ECL in glaucomatous eyes consistently with its effects in healthy eyes. Trabeculotomy produces modest ECL that is increased when MMC is used. Tube-shunt implantation leads to greater ECL that continues to increase with time. Microinvasive glaucoma surgery procedures that do not require permanent device implantation do not cause ECL, while some procedures that require permanent device implantation at the time of phacoemulsification can cause greater ECL than phacoemulsification alone.

Summary
A sufficient number of healthy CECs is required to maintain corneal health and optical clarity. Eyes with glaucoma have lower ECD than healthy eyes. Specific forms of glaucoma—typically those associated with high IOP, such as pseudoexfoliation and angle-closure glaucoma—also have lower ECD. Glaucoma therapies can also affect ECD. In general, topical IOP-lowering medical therapy has also have lower ECD. Glaucoma therapies can also affect ECD, while mixed results do not rule out a possible adverse effect of Nd:YAG laser LPI on ECD. Likewise, ALT has no significant effect on ECD, while microinvasive glaucoma surgery procedures that do not require permanent device implantation do not cause ECL, while several case reports of corneal edema and/or decompensation have been reported, the cause of which remains undetermined. Surgical procedures have the most significant effects on ECD. Phacoemulsification results in ECL in the early postoperative period that stabilizes within 1 to 3 months in both nonglaucomatous and glaucomatous eyes. Similarly, trabeculectomy leads to an acute reduction in ECD that stabilizes within the first 3 months postoperatively, and the use of MMC increases ECL. Implantation of tube-shunts into the anterior chamber causes both an initial reduction in ECD and an ongoing ECL of greater magnitude than would be expected by the attrition of aging alone. Within the family of novel glaucoma surgeries, procedures that do not require the implantation of a device typically have little effect on ECD, while procedures that involve the permanent implantation of a device tend to have greater effects on ECD which may be partially mitigated by proper device placement as far as possible from the corneal endothelial surface. In general, concerns for CEC health should be part of the decision-making process when planning glaucoma surgery for lowering IOP, with added caution in case of planned device implantation in eyes with preexisting ECL and low ECD counts at high risk for corneal endothelial decompenation.

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