Major review

Glaucoma-associated corneal endothelial cell damage: A review

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Abstract

The corneal endothelium is critical in maintaining a healthy and clear cornea. Corneal endothelial cells have a significant reserve function, but preservation of these cells is paramount as they have limited regenerative capacity. Glaucoma is a prevalent disease, and damage to the corneal endothelium may be caused by the disease process itself as well as by its treatment. The mechanisms involved in glaucoma-associated damage to the corneal endothelium need further investigation. Understanding how glaucoma and glaucoma surgery impact the endothelium is important for protecting corneal clarity and visual acuity in all glaucoma patients, including those undergoing corneal transplant. We will discuss a range of identified factors that may impact corneal endothelial cell health in glaucoma, including intraocular pressure, glaucoma medications, surgical glaucoma management, mechanical forces, and alterations in the aqueous environment.

1. Introduction

The corneal endothelium, a single layer of hexagonal-shaped cells, plays a critical role in maintaining clear vision. Its primary function is to regulate the hydration of the cornea through active ion transport, and alterations in this hydration predispose to corneal swelling and loss of clarity. Because of their critical role in vision and severely limited regenerative ability, preservation of these cells is paramount. At birth, humans start with an endothelial cell density (ECD) of 5000–6000 cells/mm² and by adulthood have 2500–3000 cell/mm² with cells arrested in the G1 phase of the cell cycle. Between the ages of 15 and 85 years, normal corneas lose 0.6% of ECD centrally per year. Measures of ECD obtained with specular microscopy imaging are a useful marker for endothelial function due to the ease of ascertainment. Unfortunately, ECD is an indirect marker and not fully representative of physiological function; however, once ECD drops below a critical level and/or under conditions of physiologic stress, the underlying functional reserve may be insufficient to maintain the appropriate corneal hydration status and corneal clarity.

Current understanding of the causative mechanisms underlying corneal endothelial cell changes that occur in...
glaucoma is deficient. Glaucoma has a worldwide prevalence of 3.5% of the population aged 40–80 years, with many of these patients undergoing varied levels of medical and surgical treatments to prevent progression of glaucoma, often with unintended and unknown consequences on the corneal endothelium. For example, higher rates of corneal endothelial cell loss have been reported with surgical glaucoma shunts, and a history of glaucoma is one of the most important factors responsible for the reduced survival of corneal grafts. Treatment of glaucoma exposes the corneal endothelium to foreign bodies, toxic compounds, and may alter the aqueous environment.

Glaucoma is associated with deleterious effects on the corneal endothelium. The underlying multifactorial influences of intraocular pressure (IOP), glaucoma medications, surgical management, mechanical forces, and alterations in the aqueous environment will be reviewed in this article.

2. Intraocular pressure

IOP, its elevation a hallmark of nearly all glaucoma presentations, has been studied extensively in relationship to the health of the corneal endothelium and accelerated loss of corneal endothelial cells in glaucoma. Although there may be intrinsic differences in endothelial cell susceptibility in different types of glaucoma patients, the following studies support that the elevations in pressure result in damage to the corneal endothelium.

Gagnon and colleagues examined the relationship between corneal ECD and multiple types of glaucoma and found ECD to be lower in glaucoma patients than in controls, with an inverse relationship between IOP and ECD. They presented 3 hypotheses of why glaucoma patients had greater endothelial cell loss: 1) direct compression from higher IOP, 2) congenital alteration of the endothelium and trabecular meshwork, and 3) glaucoma medication toxicity. Based on their findings, they proposed that the level of IOP elevation was more important than the duration of glaucoma and, therefore, patients with well-controlled glaucoma would be at lower risk for endothelial cell damage.

To evaluate the effect of IOP on ECD further, Cho and colleagues compared the ECD in normal nonglaucoma patients, primary open-angle glaucoma patients, and normal-tension glaucoma patients. None of these patients had undergone intraocular or corneal surgery prior to or during the study. They found no differences in ECD between the normal and normal-tension glaucoma patients; however, a statistically significant 13% reduction of ECD in the untreated primary open-angle glaucoma patients existed in comparison to controls. None of the patients included in this study were using glaucoma medications, indicating that the differences observed most likely were attributable to the IOP differences.

There also have been comparisons of ECD loss between glaucoma patients and ocular hypertension patients. In the Cornea Donor Study, Sugar and colleagues reported that a history of glaucoma or ocular hypertension in the graft recipient was strongly associated with the graft failure. In a comparison of juvenile open-angle glaucoma versus ocular hypertension, decreased ECD was detected in juvenile open-angle glaucoma, whereas ECD in the ocular hypertension group did not differ statistically from healthy controls; however, IOP was not compared between the groups in this study. Consequently, differences in the observed ECD between juvenile open-angle glaucoma and ocular hypertension patients might be due to differences in IOP between the groups.

Congenital glaucoma is another type of glaucoma that often presents with elevated IOP, and even after combined trabeculotomy-trabeculectomy surgeries in 299 eyes of 157 patients, normal corneal clarity was achieved only in 62.4% of eyes. In the studies of congenital glaucoma, however, it is impossible to determine if the duration of elevated IOP or the presence of a tube leads to persistent corneal dysfunction and impaired clarity.

There are additional types of glaucoma that are also associated with increased IOP. These include pseudoexfoliation syndrome, pseudoexfoliation glaucoma, and iridocorneal endothelial syndrome; however, the preceding discussion of IOP has omitted reference to these diseases owing to the endothelium’s direct involvement in the disease process. Eyes with pseudoexfoliation syndrome and pseudoexfoliation glaucoma have decreased ECD, and the endothelial cell loss is greater in those with pseudoexfoliation glaucoma compared to pseudoexfoliation syndrome; however, it is impossible to determine whether elevated IOP in pseudoexfoliation glaucoma is involved in the mechanism of endothelial cell injury or whether corneal endothelial cell loss is related directly to the focal accumulations of pseudoexfoliation material. Iridocorneal endothelial syndrome is similar in that the endothelium takes on abnormal epithelium-like changes, and the glaucoma and IOP elevation are likely not the inciting insults to the corneal endothelium.

These differences suggest that, although IOP is an important risk factor in endothelial cell loss, it is not the sole factor. It is reasonable to infer from these studies that endothelial cells in various types of glaucoma may have different susceptibilities to IOP injury, just as glaucoma progression occurs at different IOPs depending on the type of glaucoma (e.g., normal-tension glaucoma vs primary open-angle glaucoma).

Another condition studied for its impact on ECD is angle-closure glaucoma. Angle-closure glaucoma patients often present with much higher elevations in IOP and logically should manifest damage to the corneal endothelium if elevated IOP mediates endothelial cell damage. Sihota and colleagues looked at the patients with acute, subacute, and chronic subtypes of primary angle-closure glaucoma (PACG) and compared the endothelium to both control patients and the patient’s fellow eye (with occludable angles, but without glaucoma). They found that acute PACG had significantly decreased ECD compared to the other 3 groups and 35.1% lower ECD compared to age-matched controls. Tham and colleagues also found that acute PACG patients had an 11.6% reduction in ECD compared to their chronic angle-closure counterparts. They also demonstrated that the longer the duration of the acute attack, the greater the loss of ECD in that study. Specifically, those with acute PACG attacks less than 72 hours had ECD measurements of 2016 ± 306 versus 759 ±
94.4 cells/mm² in those with attacks lasting more than 72 hours. Another study also found that acute attack durations over 12 hours had a 7.3-fold greater risk of central ECD < 2100 cells/mm², which was the lowest quartile in that study. Acute PACG patients included in these studies often presented with IOP exceeding 40 mm Hg, with some presenting with IOP as high as 73 mm Hg. Chronic PACG can also present with elevated IOP but to lesser magnitudes. Yet, even chronic PACG patients manifest decreased mean ECD measurements by 9.4% in comparison to the control eyes. Although these investigations support the hypothesis that increased IOP contributes to the endothelial cell loss, angle closure may also cause trauma to the endothelium by iridocorneal touch or disruption of aqueous flow and therefore inducing hypoxia and reducing nutritional support of the endothelium.

There is additional evidence that elevated IOP damages the corneal endothelium in patients who undergo penetrating keratoplasty (PK). In 1 study comparing patients with and without a glaucoma history undergoing PK, postoperative IOP elevation had a significant effect on ECD after a PK, whereas the presence of a glaucoma history was not associated with a significant difference in ECD; however, the number of glaucoma patients was low in this study. Additional investigation is needed with greater patient enrollment to determine the validity of these findings and confirm whether transplanted endothelium is more vulnerable to elevated IOP than native endothelium.

3. Medically-treated glaucoma

One area of research interest is how medically-treated glaucoma affects the corneal endothelium. Patients with glaucoma often remain on long-term therapy with varying numbers of pressure-lowering glaucoma drops. These medications have been studied extensively and have been shown to cause molecular changes in experimental models as will be discussed in the following section; however, glaucoma medications have not been linked directly with endothelial cell loss.

From a molecular perspective, however, glaucoma medications do cause changes in corneal endothelial cells. Dilutions of 1/100, 1/1,000, and 1/10,000 of betaxolol, timolol, levobunolol, carteolol, dipivefrin, dorzolamide, brinzolamide, latanoprost, unoprostone, and pilocarpine have all increased intracellular calcium in bovine corneal endothelial cells, whereas brimonidine decreased intracellular calcium concentrations. These deviations in calcium mobility may alter endothelial function, as calcium mediates endothelial cell apical junctions, paracellular calcium permeability, and subsequent corneal swelling. A follow-up study by Wu and colleagues found among the same medications that 1/100 dilutions of betaxolol, brimonidine, dorzolamide, dipivefrin, latanoprost, and unoprostone caused the release of lactate dehydrogenase, a marker of cell lysis. Other medications assayed in that study, including dilutions of the preservative benzalkonium chloride, did not affect lactate dehydrogenase release.

Clinically, studies have not been able to detect endothelial cells loss due to glaucoma medications; however, such studies have been limited by their short duration in comparison to the many years of medication use by glaucoma patients. Larger and longer studies of glaucoma medications might be required to detect possible effects on corneal endothelial cells that have not been recognized to date.

Dorzolamide lowers IOP by inhibiting carbonic anhydrase isozyme II, which is present not only in the aqueous-producing ciliary body, but also in corneal endothelial cells. In studies of dorzolamide, no difference in ECD loss or corneal thickness was observed in comparison to topical beta-blocker drops. A 1-year randomized controlled trial of topical dorzolamide, timolol, or betaxolol drops in patients with normal corneas showed ECD loss of 3.6%, 4.5%, and 4.2%, respectively, which were not found to be statistically different. There was no control group in this study for comparison. Theoretically, carbonic anhydrase inhibitors such as dorzolamide may affect pump function due to the presence of carbonic anhydrase isozyme II in these cells, but the authors suggest that the functional reserve of the endothelial cells prevents a clinically significant effect. Since this study included only normal corneas, these findings cannot be generalized to patients with low ECD (300–500 cells/mm²), as this inhibition may be more clinically significant due to decreased functional reserve. Another 1-year randomized controlled trial of latanoprost, latanoprost-timolol, or timolol also did not find any differences from baseline endothelial measurements or among treatment groups. Another study of normal corneas found no difference in the ECD, percent hexagonal cells, or coefficient of cell variation of cell area in patients treated with latanoprost versus latanoprost and brinzolamide, another carbonic anhydrase inhibitor.

In longer follow-up studies, the results were similar. Baratz and colleagues studied glaucoma patients enrolled in a 6-year ocular hypertension treatment study group that underwent yearly specular microscopy. In that study, no differences were detected in ECD, percent hexagonal cells, or coefficient of cell variation of cell area between patients using topical glaucoma medications and untreated controls. The 0.68% per year rate of endothelial cell loss in the medically treated group was similar to the 0.6% yearly loss reported in normal corneas. In studies evaluating recipients of Descemet stripping endothelial keratoplasty (DSEK), Descemet stripping automated endothelial keratoplasty (DSAEK), and PK with no glaucoma, medically managed glaucoma, and surgically managed glaucoma, 5-year graft survival did not differ between patients with medically managed glaucoma and patients with no glaucoma.

4. Surgically treated glaucoma

Patients with severe or uncontrolled glaucoma will often undergo surgery for management of IOP. Glaucoma surgical procedures including trabeculectomy, Ahmed glaucoma valve implants (New World Medical), Molteno implants (IOP, Inc. and Molteno Ophthalmic Limited), Baerveldt implants, and EX-PRESS shunts (Alcon) are used widely to control IOP. An unintended consequence of glaucoma surgery is the progressive loss of corneal endothelial cells that can lead to corneal decompensation. Corneal complication rates of 8%–29% after aqueous shunt
implantation are reported. A comparison of endothelial cell loss rates documented in the various studies can be found in Table 1.

In a 12-year study, a progressive decline in ECD was reported following Ahmed glaucoma valve implantation, with 18.6% mean endothelial cell loss. The loss was greatest (22.6%) in the superior temporal quadrant (where the tube was present). This decline is clinically important as the most frequent complication of Ahmed glaucoma valve implantation was corneal decompensation, which occurred in 27% of eyes. This is in comparison to late postoperative persistent corneal edema in 16% of patients undergoing Baerveldt implantation in the Tube Versus Trabeculectomy study. Initial hypotheses proposed to explain the endothelial loss observed after aqueous shunts included jet flow around the tube end, inflammation, intermittent tube-corneal touch, and foreign body reaction. Other intraocular surgeries, such as cataract surgery and vitreoretinal surgery, lead to endothelial cell loss; however, this ECD loss typically occurs as a 1-time event, in contrast with the progressive ECD loss observed after glaucoma drainage device implantation.

Data regarding other glaucoma surgeries and corneal endothelial cell changes are also available. In comparison to Ahmed glaucoma valve implants, Molteno implants showed similar endothelial cell loss at 24 months after surgery with 12.37% ECD loss for Molteno and 11.52% for Ahmed implants. In a study of Baerveldt implants, the rate of central ECD loss was 4.54% per year. EX-PRESS shunts have been observed to have no change in ECD loss after 3 months of follow-up, and the authors of that study propose that EX-PRESS shunts benefit recipients due to decreased invasiveness and shorter operating times. However, operating time is negligible compared to the duration the implant will remain in the eye; thus, studies with longer follow-up are needed.

Tube shunts appear to have greater reported endothelial cell loss compared to trabeculectomy. Trabeculectomy was observed to have a smaller decline in ECD of 3.2% over 12 months compared to 12.3% after Ahmed valve implantation. Both procedures attained the same postoperative IOP but not the same degree of risk to the endothelium. Although trabeculectomy appears to be more protective of corneal ECD than glaucoma drainage device implantation, single deep sclerectomy showed even lower levels of endothelial cell loss in comparison to trabeculectomy. Theoretically, a deep sclerectomy imparts less trauma to the endothelium by avoiding entry into the intraocular space, which may explain the lower reported rate of 2.6% ECD loss over the 1-year follow-up.

One complicating factor of glaucoma surgery is the use of mitomycin C (MMC) to help inhibit episcleral fibroblasts and preserve filtering blebs. MMC exhibits cytotoxic effects, and damage to the corneal endothelium increases with higher concentrations. In cases of trabeculectomy without MMC, with low concentration MMC (0.2 mg/mL), and with high concentration MMC (0.4 mg/mL), endothelial cell loss after 3 months was 3.73, 13.90, and 14.52%, respectively. Despite the application of MMC externally, some MMC reaches the aqueous. Endothelial cell loss of 9.5% was detected at 3 months following trabeculectomy with 0.2 mg/mL MMC and did not significantly progress at 12 months, suggesting a static toxic effect of MMC on the corneal endothelium. The use of viscoelastics during surgery may help reduce endothelial cell loss when MMC is employed. In a study of trabeculectomy with MMC, ECD loss at 3 months with sodium hyaluronate (Healon; Pharmacia) use during MMC application was 2.5%, compared to 7.7% when sodium hyaluronate was not used.

5. Glaucoma and graft survival

A special case in the discussion of corneal endothelium and glaucoma is the impact on corneal transplant survival. As keratoplasia technology and techniques have advanced, multiple studies have looked at the impact of glaucoma and its management on graft survival. In the Cornea Donor Study, Sugar and colleagues noted that a history of glaucoma or ocular hypertension was strongly associated with PK graft failure. This finding was in agreement with the Collaborative Corneal Transplantation Studies, which found higher graft failure rates in eyes with preoperative glaucoma (48%)
compared to eyes without preoperative glaucoma (29%). In the 10-year report of the Cornea Donor Study, the rate of graft failure in PK recipients with glaucoma stabilized after 5 years postoperatively. Glaucoma surgery appears to confer risk for graft failure in transplant recipient in the studies of DSEK, DSAEK, and PK. Conversely, no increased risk for graft failure was observed in keratoplasty recipients with medically managed glaucoma.

Just as technology and techniques have advanced in corneal transplantation, so too have glaucoma surgical approaches in the era of minimally invasive glaucoma surgery. While these approaches warrant further investigation, they may offer promise for decreasing the rate of corneal graft failure in glaucoma patients. Kusakabe and colleagues reported that patients who underwent trabeculotomy after PK showed similar rates of endothelial cell loss compared to PK patients without glaucoma. Ates and colleagues found that EX-PRESS shunt use in 15 post-PK patients over an average follow-up of 1 year was associated with the stable biomicroscopic findings and clear grafts.

6. Mechanical damage

One hypothesis raised by several studies to explain the ECD loss associated with glaucoma surgery is that the implantation of a tube shunt into the anterior chamber introduces mechanical forces that result in endothelial cell loss, either directly via contact or indirectly through flow turbulence. Many studies have attempted to look at this interaction. Both timing of tube shunt implantation and tube-cornea proximity have been investigated. Kwon and colleagues found that in patients with PK and tube implantation, the tube-first group was 4.7 and 3.8 times more likely to have earlier graft failure than PK-first and simultaneous PK-tube groups, respectively; however, 100% of tube-first patients had preexisting glaucoma, and uncontrolled IOP necessitating glaucoma surgery may account for this difference. A 3-year study of Baerveldt tubes by Tan and colleagues found that endothelial cell loss was greatest when the tube-cornea distance decreased and in the quadrant containing the tube. ECD loss occurred at a yearly rate of 4.54% centrally and 6.57% in the peripheral quadrant, on average. In cases with shorter tube-cornea distances as measured by anterior segment optical coherence tomography, the observed ECD loss was 6.20% centrally and 7.25% in the peripheral quadrant, compared to 4.11% centrally and 5.77% in the peripheral quadrant ECD loss in eyes with longer tube-cornea distances. Another study of Ahmed valve implants found similar results with greater ECD preservation in eyes with a greater tube-cornea distance. In contrast, Mendrinos and colleagues used anterior segment optical coherence tomography to measure tube-cornea distance but did not find any association of endothelial cell loss with tube-cornea, tube-iris, or intracameral length of the drainage tube. That study also compared endothelial cell loss centrally and peripherally but did not find a difference in cell loss (7.9% ± 2.5% and 7.5% ± 2.4%, respectively).

Although the aforementioned studies suggest that there is an association between endothelial cell loss and tube position, the position of the tube in relation to the cornea may not be static and may migrate. In a study of 70 eyes with Baerveldt tubes, the tube-cornea distance decreased significantly over 24 months in eyes with tubes placed freely in the anterior chamber but did not decrease in those with transiridal tube placement. Another study that investigated anterior chamber Ahmed glaucoma valve implants followed over 12 months reported a mean decrease of the tube length by 0.20 mm; a mean increase of the tube-iris distance by 0.11 mm; and a mean decrease of the tube-corneal angle by 6.7°. Eyes with a history of uveitic glaucoma and post-PK eyes were associated with the greatest change of intracameral tube length. These studies show changes over time, but in a few cases, tube movement may be more dynamic. There have been case reports of Ahmed tube movement by 3–4 mm within the eye during various gazes, although no corneal damage was reported in those cases.

7. Aqueous environment

Corneal endothelial cells are bathed in aqueous humor, and alterations in this environment could disrupt the endothelium, by both withdrawing critical nutrients and introducing proinflammatory and deleterious proteins. The study of differences in the glaucoma aqueous environment is just beginning, and early investigations indicate that differences are present in the aqueous composition of glaucoma patients. In patients with glaucoma shunt devices (9 Ahmed and 2 Baerveldt) versus control patients, glaucoma patients had significantly higher levels of 13 proteins known to have roles in mediating oxidative stress, apoptosis, inflammation, or immunity (Celloxin, plasminogen, angiotensinogen, apolipoprotein A-II, beta-2-microglobulin, dickkopf-3, pigment epithelium-derived factor, RIG-like 7-1, afamin, fibronectin 1, apolipoprotein A-I, activated complement C4 protein, and prothrombin). Notably, all these proteins, except complement C4, are plasma proteins, suggesting that glaucomatous disease states may be associated with a breakdown in the blood-aqueous barrier. A follow-up study by the same group expanded their analysis to include patients who underwent trabeculectomy and EX-PRESS trabeculectomy, as well as more patients with Baerveldt and Ahmed implants. Protein levels in aqueous humor collected 2–12 years postoperatively were 10-fold higher in the tube shunt–based surgeries, and 5-fold higher in the trabeculectomy and EX-PRESS surgery eyes, when compared with controls undergoing cataract surgery without prior intraocular surgeries. In total, 514 proteins were identified with aqueous humor concentrations that differed between the control, aqueous shunt, and trabeculectomy shunt samples. The concentrations of nearly half of the identified proteins differed significantly between the aqueous shunt and trabeculectomy groups. The authors argue that the alterations in the aqueous environment, not mechanical forces from the tube, cause the increased risk of decompensation in glaucoma surgery patients and cite those with pars plana aqueous shunts have similar risks of decompensation as those with anterior chamber aqueous shunts. The major and critical weakness of these recent studies is that control samples came from cataract surgery
patients rather than nonsurgical glaucoma patients. Consequently, the differences observed may be due to glaucoma, glaucoma surgery, or both. Another study by O’Callaghan and colleagues found decreased levels of matrix metalloproteinases in glaucoma patient aqueous, although they did not report the presence of previous glaucoma surgeries.33

8. Conclusion

Glaucoma and its management may have deleterious effects on the corneal endothelium. There is still much more to learn about how increased IOP, mechanical forces, and the aqueous environment contribute to corneal endothelial cell loss broadly observed in the milieu of glaucoma treatment. A history of glaucoma surgery poses a particularly significant risk to corneal endothelial cell health and cornea transplant graft survival. Targeted approaches investigating the effect of protein-mediated changes in the aqueous on corneal endothelial cells and the surrounding environment are promising avenues to pursue a deeper understanding of glaucoma-associated endothelial cell damage. As discussed in this review, many studies are limited by short follow-up periods, inability to isolate a single variable, and variation in medical and surgical treatment of glaucoma. Although research design is beyond the scope of this discussion, high-quality studies utilizing control groups and support from in vitro models that manipulate single variables will be important in developing a greater understanding of corneal endothelial cell damage in glaucoma. Understanding these mechanisms is vital to the prevention of corneal decompensation, prevention of graft failure and subsequent repeat surgeries, and maintenance of clear vision.

8.1. Methods of literature search

In preparing this article, a search was performed for all English publications with the following 3 searches: ["Glucoma"[Majr] AND "Endothelium, Corneal"[Majr]] OR ["corneal endothelium"[ti] OR "corneal endothelial"[ti]] AND glaucoma [ti]], ["Glucoma"[Mesh] AND "Endothelium, Corneal" [MESH]], ["corneal endothelium" OR "corneal endothelial"] AND glaucoma]. From the searches, all articles pertaining to the relevant topic were included in this review. No constraints were placed on publication date or publication journal.

9. Disclosures

The authors have no commercial or proprietary interest in any concept or product described in this article.

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