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The glaucoma - cornea interplay: A review

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Abstract
Glaucoma, the leading cause of irreversible blindness worldwide, and the cornea, has a quite complex, bidirectional relationship. The diagnosis and management of glaucoma is partly affected by corneal properties and changes such as corneal thickness, biomechanics and prior surgery. Similarly, glaucoma, the disease itself, at its lines of management, whether medical treatments, laser modalities, or incisional surgeries can alter the cornea, in different ways. Following the withdrawal of The CyPass Micro-Stent, a promising minimally invasive glaucoma implant, after concerns about its effect on the corneal endothelium, the influence of glaucoma surgeries, particularly hardware involving surgeries, on the corneal endothelium has become an area of growing interest. Corneal transplant surgeries that may be needed following glaucoma surgery related endothelial decompensation would represent an extra burden in the setting of developing countries with limited resources. Furthermore, these surgeries are more likely to fail, when glaucoma co-exists.

Keywords: Glaucoma, cornea, endothelium, specular microscopy.

Introduction
Since the landmark Ocular Hypertension Treatment Study (OHTS) highlighted the importance of Central Corneal Thickness (CCT) as a risk factor for glaucoma development, the interaction between glaucoma, the leading cause of irreversible blindness worldwide [1], and the cornea, has been extensively studied [2]. Recently, the COMPASS-XT demonstrated a significant rates of endothelial cell loss (ECL) following CyPass micros tent implantation, resulting in its market withdrawal [3]. The glaucoma-cornea interplay seems to be quite complex and essentially bidirectional.

Glaucoma
Glaucoma refers to a heterogeneous group of conditions in which the level of intraocular pressure (IOP) is a major risk factor for the loss of retinal nerve fiber layer and the occurrence of characteristic optic disc changes, causing retinal ganglion cells death and corresponding visual field loss. [4] So far, the only proven way to prevent glaucoma progression is IOP lowering, which can be achieved by methods of medical treatment, laser modalities, and incisional surgeries [5]. The field of glaucoma surgery has recently significantly expanded. Figure (1) summarizes current different glaucoma surgical options.

The Cornea
The cornea is the anterior transparent part of the eye's outer coat. The corneal layers are, from superficial to deep: Epithelium, Bowman's layer, stroma, Dua's layer, Descemet's membrane (DM), and endothelium [6].

The corneal endothelium
The cornea is internally lined by a single layer of polygonal endothelial cells, that were traditionally believed to be quiescent, lacking the capacity to regenerate, and, when injured, their defects are compensated for by the migration and enlargement of adjacent cells. However, ex vivo and *in vitro* growth of endothelial cells has been demonstrated. It's believed that progenitor-like stem cell population of adult corneal endothelial cells exists near Schwalbe line at the endothelium-trabecular meshwork transition zone, with limited capacity of proliferation [7]. Endothelial cells are vital for maintaining corneal transparency and therefore corneal function.

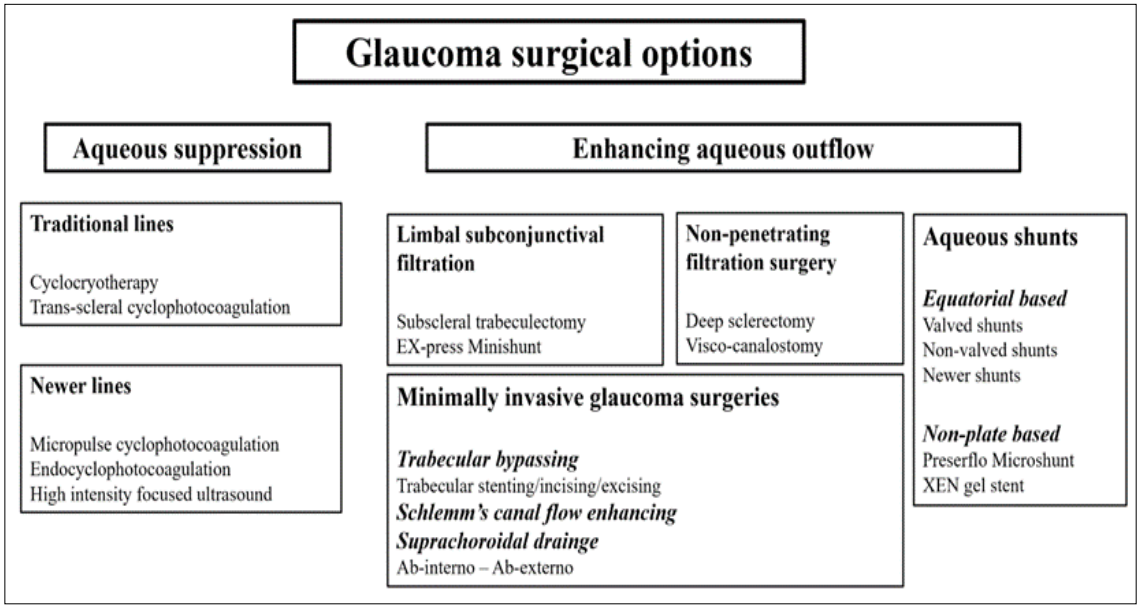

Fig 1: Overview of glaucoma surgical options

The balance between the passive diffusion and active removal of fluids across the corneal endothelium is essential to achieve a certain level of corneal hydration, by a mechanism known as the pump-and-leak hypothesis [8].

Assessment of corneal endothelium

From basic examination, to complex imaging techniques, there are several methods to assess the health status of corneal endothelial cell. On examination, areas of diffuse or localized corneal thickening correspond to endothelial cell dysfunction. The presence of guttata implies areas of DM excrescences and cell dropout. The standard technique for endothelium visualization using slit lamp is specular reflection [9].

Specular microscopy (SP) is the most widely used modality to obtain endothelial cell images that are automatically processed and analyzed to give a quantitative report of corneal endothelial parameters (CEP) [10-12] There are three basic CEP measured by SP: *Endothelial cell density (ECD)* which is the cell count per square millimeter, with normal values between 2200 to 3200 cells/mm2. *Coefficient of variations (CV)* is a measure of uniformity in size, estimated by dividing standard deviation of mean cell area by mean cell area, and typically normally measures 0.25. With increasing endothelial cell damage, there will be more variability of cell area, resulting in higher CV values, which is known as polymegathism. *Hexagonality* (HEX%), is a measure of the hexagonal morphology of the cells, and it's equal to (Number of hexagonal cells/Number of all cells), with normal values of 70-80%. As the cells are damaged, they lose their hexagonal structure and become pleomorphic, a phenomenon known as polymorphism.

One problem with SP is that the scanned area is actually a small fraction of the area it represents, whether central or peripheral cornea, with the inherited problems that come with any sampling process [13]. Wide field SP is a promising step towards alleviating such sampling-related errors [14]. Doughty *et al*. [15]. Estimated a number of 75 scanned cells by SP as the threshold for being adequately representing the corneal area studied, while van den Berg *et al*. [16] suggested a minimum of 425.2 cells to represent the whole cornea. Another issue is that significant differences do exist between the outcomes of different SP devices [17-19]. In clinical trials with endothelium related outcomes, SP images are ideally analyzed by an independent reading center. It was estimated that ECD data from a multicenter clinical trial has an inherent variability of ±10% [3].

It's generally believed that when endothelial cell dysfunction happens, the values of CECD and HEX decrease while CCT and CV increase. Mac Rae *et al*. [20] suggested that pleomorphism and polymegathism indicate that the cornea is under stress, whereas ECD decrease indicates that cell death has happened. ECL refers to reduction of CECD rather than change in CV or HEX.

In addition to SP, a change in baseline pachymetry is a very accurate way of assessing endothelial cell function. Ultrasound pachymetry, corneal topography and anterior segment optical coherence tomography thickness maps can also help to find focal or variable areas of corneal thickening that can localize to areas of focal ECL. [21] *In vivo* confocal microscopy (IV-CM) is can visualize the corneal endothelial cells, especially in the presence of corneal cloudiness [22].

Etiology of endothelial cell dysfunction

Corneal endothelial dysfunction can be primary or secondary to other conditions. The most common cause of primary endothelial dysfunction is Fuch's endothelial dystrophy [22]. Secondary causes include trauma; either accidental or surgical, inflammatory conditions e.g. toxic anterior segment syndrome, infections e.g. herpetic keratitis, topical medications e.g. antifibrotic agents, and systemic medications e.g. Amantadine and Bisphosphonate [23].

The interplay

Corneal thickness and glaucoma

The OHTS has recognized CCT as a significant risk factor for progression of ocular hypertensive patients to POAG [2]. However, there is no strong evidence to consider CCT as an independent risk factor. Although CCT adjusted IOP algorithms are widely used by clinicians, the most recently published guidelines of the European Glaucoma Society mentioned that they are not validated and therefore not recommended [24].

Corneal biomechanics and glaucoma

The Ocular Response Analyzer (ORA) is a non-contact tonometer that measures the corneal response to indentation by a rapid air pulse. Corneal Hysteresis (CH) indicates the viscous damping in the cornea. Corneal deformability can potentially act as a surrogate to how the back of the eye behaves in response to different levels of pressures, which in part explains why ocular hypertensives without glaucoma and normotensive glaucoma, on the other hand, exist [25].

Corneal diseases and glaucoma

Corneal diseases can cause secondary glaucoma, of either the open and closed angle type. An example is ocular herpetic infection, which can present with early ocular hypertension due to trabeculitis and trabecular meshwork blockage by debris, or later, due to steroid treatment. Furthermore, bacterial and fungal keratitis can lead to glaucoma through inflammatory changes leading to Peripheral Anterior Synechiae (PAS) formation and/or pupillary block [26].

Corneal surgeries and glaucoma

The diagnosis of glaucoma following kerato-refractive surgeries, as they change corneal thickness and alter its biomechanics, can sometimes be a challenge. Following LASIK, for example, high IOP can cause fluid to be entrapped inside corneal stroma, a condition known as interface fluid syndrome. Similar challenges exist with corneal transplant surgeries, either penetrating, or lamellar [27].

Effect of glaucoma on the cornea

IOP and cornea

IOP itself contributes to maintaining corneal clarity by producing an outward compressive force that keeps the stromal layers compact. During hypotony, the cornea can become edematous because this compressive effect is lost. On the other hand, with acutely elevated IOP, microcystic epithelial edema results when high IOP drives fluid across the loose endothelial junctions [28]. In a similar fashion, studies reported significantly worse CEP in other glaucoma subsets e.g. pseudo exfoliation and uveitis [29, 30]. Additionally, eyes with normotensive glaucoma and pseudo exfoliation are known to have thinner cornea [31].

Anti-glaucoma medications and cornea

Prostaglandin analogues were associated with lower CCT, and may be, interestingly, related to keratoconus progression. CH seems to be significantly lower in PGA-treated eyes. Carbonic anhydrase inhibitors pose a risk of decompensation in corneas with borderline endothelium [32]. The evidence regarding the effect of B-adrenergic blockers and alpha adrenergic agonists on corneal endothelium is contradictory [32].

Glaucoma lasers and cornea

Most glaucoma laser treatments are generally considered cornea friendly options, in comparison to incisional surgeries.

Laser iridotomy

Laser peripheral iridotomy, using either argon or Nd: YAG laser, showed no clinically significant effect in most reports. However, few reports mentioned the occurrence of a focal ECL confined to the area of laser treatment, especially in eyes with narrow angles [33].

Laser trabeculoplasty

Argon laser trabeculoplasty studies have consistently reported no ECL up to 1 year after the procedure. Data regarding selective laser trabeculoplasty studies are inconclusive, but there are rare reports of acute corneal edema associated with subsequent corneal thinning and hyperopic shift, following treatment. No changes in ECD have been reported after externally delivered micro pulse trabeculoplasty [34].

Laser cyclophotocoagulation (CPC)

Data regarding corneal endothelial changes following conventional Trans scleral CPC are generally scarce, however, in the context of previous corneal transplant, CPC related corneal edemas and graft failures were reported. No significant change in corneal endothelium was found in the short term following micro pulse CPC, or Endocyclophotocoagulation treatments [35].

Glaucoma surgery and cornea

The effect of glaucoma surgery on the cornea, especially the corneal endothelium, is an interesting area of ongoing research, especially with current advances in the techniques of glaucoma and corneal transplant surgeries. The World Glaucoma Association guidelines list ECD as a safety outcome measure in glaucoma surgery trials. [36]. The mechanisms are numerous, including events related to the surgery itself, e.g. instrumentation, prolonged anterior chamber (AC) shallowness and endothelial contact with iris or lens. However, it's believed that a continuous cell loss can also occur over time, especially with hardware involving surgeries.

Trabeculectomy and anti-metabolites

Sub scleral trabeculectomy (SST) is a known cause of ECL. The most devastating effect to the cornea of is a flat chamber postoperatively [37]. If the lens touches the central cornea, over 50% of the endothelial cells can be lost. Combined phacoemulsification with SST does not produce significantly greater ECL than either phacoemulsification alone or SST alone, either one site or two site combined surgery. Whether the usage of the EX-PRESS minishunt makes SST more endothelium friendly or not is largely debatable [38, 39]. SST augmented with the antimetabolite mitomycin-C (MMC) was associated with more ECL compared with SST without MMC [40].

Non-penetrating glaucoma surgery

While these surgeries are associated with more risk of developing DM detachment that can cause focal corneal edema, they were found to have less ECL, compared to SST, probably thanks to avoiding some of the immediate postoperative complications of SST [41].

Glaucoma tube shunts

Corneal complications of glaucoma tube shunts are arguably one of the most concerning aspects of these devices. In a report of the long-term follow-up of 60 eyes that had Ahmed glaucoma valve (AGV) implantation, corneal decompensation or corneal graft failure was the commonest adverse outcome [42]. The FDA considers more than 30%

loss of ECD at 24 months as significant for implantable glaucoma devices [43].

Although the mechanism of ECD loss is not precisely understood. It's believed that continued small movements of the tube element relative to the cornea (micromotion) transmitted from repeated minor displacement of the plate element during eye movement play a major role. This gradual attrition may be superimposed on significant intraoperative and early post-operative endothelial damage from macroscopic contact between the implant and the cornea in association with poor tube positioning or AC shallowing. Another suggested mechanism could be focal change in AC dynamics, aqueous environment and corneal nutrition in the vicinity of the tube, not having as enough aqueous contact as the rest of the cornea, rather than the mere existence of foreign material close to the endothelium [44, 45].

Hau *et al*. [46] found a central ECL rate of 36.8% at 5 years, with an average yearly rate of 7.4% when Baerveldt glaucoma implant (BGI) was implanted in the AC. Tube insertion position in relation to scleral spur was identified as the strongest influencing factor on CEP. An older study by that group [45], found that central ECL in eyes that had glaucoma tube shunt implantation was related to the time passed since surgery, the degree of PAS in clock hours and the number of previous operations. The landmark studies, Ahmed versus Baerveldt Study and Ahmed Baerveldt Comparison Study (ABC/AVB), had an average incidence rate of 12% persistent corneal edema at 5 years post-operatively, with no significant difference based on device type [47-49]. Similarly, the location of the tube is believed to have a significant effect on the magnitude of tube shunt related ECL. Zhang *et al*. [50] found less ECL in sulcus implanted AGV, compared to those implanted in the AC. Additionally, Tojo *et al*. [51] found a better endothelial profile in eyes where BGI was implanted in the vitreous cavity, compared to AC implantation.

The Paul glaucoma implant (PGI) is a recent glaucoma drainage device that comes with a smaller tube, which theoretically can be more endothelium-friendly, but no data about their endothelium safety profile has come to light yet.

Novel non-plate based aqueous shunts

Because they are made from different material and come with a smaller diameter, the XEN gel implant (XEN) and Preserflo MicroShunt (PMS) are thought to be more endothelium friendly, compared to plate based tube shunts. Steindor *et al*. [52] reported no significant ECL with PMS over 20 months follow up. Ibarz-Barberá *et al*. [53] reported a significant reduction of central CECD at 12 months (7.4%). Oddone *et al*. [54] reported significant ECL of 5.6% at 6 months following XEN surgery. Gillmann *et al*. [55] found no difference in ECL rates after combined phaco-XEN compared to standalone phacoemulsification at 2 years. There are sporadic reports of corneal decompensation following PMS and XEN implantation, which were explained by the close contact with the corneal endothelium and device migration [56, 57].

Minimally invasive glaucoma surgeries (MIGS)

Since the CyPass market withdrawal, the effect of MIGS, particularly those involving hardware implantation, on corneal endothelium has become a great concern. These procedures are usually combined with phacoemulsification.

A recent study that pulled data from different pivotal trials compared the endothelial safety profile of iStent inject, Hydrus Micros tent (HMS) and CyPass, found that iStent inject had the most favorable endothelial profile, with no difference compared to cataract surgery alone at all time points up to 5 years postoperatively. Both CyPass and HMS showed significant differences in ECL and proportion >30% from baseline compared to cataract surgery alone. While CyPass showed progressive ECL beyond 3 years, implying a device-related mechanism of cell loss, the rate of ECL with HMS was comparable to the control group (cataract surgery) beyond 3 months (aging loss), and implying long term device tolerability [58].

Cataract surgery

With the results of the landmark EAGLE study coming to light, the role of cataract surgery as a part of the glaucoma surgical armamentarium has greatly expanded [59].

Reported rates of ECL following modern uneventful cataract surgery varies from 0 to 20% [60, 61]. Some reports found no significant difference between ECL following phacoemulsification and extra-capsular cataract extraction [62]. The mechanisms of ECL following cataract surgery are numerous, including mechanical injury caused by AC instrumentation, AC manipulation of a lens nucleus, ultrasound time and power, heat generation, prolonged intraocular irrigation and the type of ocular viscoelastic devices used [62, 63]. The placement of posterior chamber IOL, independent of its precise location and method of fixation does not appear to make a significant effect on CECD [63, 64].

Summary

Upon managing glaucoma, the status of the cornea should be taken into consideration, particularly when considering surgical lines of treatment. Although currently available techniques provide valuable insight regarding the assessment of corneal status, including the corneal endothelium, generated data should be approached with caution. With the advances in glaucoma and corneal transplant surgeries, improvement of the endothelial imaging techniques, as well as development of more cornea friendly glaucoma surgeries, are much needed.

Conclusion

In managing glaucoma, the corneal status must be carefully considered, especially when surgical options are on the table. While available assessment techniques provide valuable insights into corneal health, their data should be interpreted cautiously. Advances in glaucoma and corneal transplant surgeries, as well as improved endothelial imaging techniques, are crucial. Additionally, developing more cornea-friendly glaucoma surgeries is essential to minimize complications and preserve corneal function. This comprehensive approach ensures better outcomes for patients, balancing glaucoma treatment efficacy with the preservation of corneal integrity.

Conflict of interest

Not available

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