Irvine and Kaufman (1969) were the first to describe an association between penetrating keratoplasty (PK) and glaucoma. Post-penetrating keratoplasty glaucoma (PPKG) is one of the most challenging problems because of its frequent occurrence, difficult diagnosis, recalcitrant nature, irreversible visual loss due to damage to optic nerve as well as the donor endothelium and management difficulty.

**Definition**

Post-PK glaucoma is defined as an elevated intraocular pressure (IOP) greater than 21 mmHg, with or without associated visual field loss or optic nerve head changes, at any time during the post operative period.

**Magnitude of the problem**

Rise in IOP following keratoplasty has been reported to be a biphasic phenomenon. The incidence of glaucoma after keratoplasty varies from 9% to 31% in the early postoperative period and 18% to 42% in the late postoperative period.

**Full thickness keratoplasty vs. lamellar keratoplasty**

Since there is no disruption of Descemet’s membrane in deep anterior lamellar keratoplasty (DALK), there should be no distortion of the anterior chamber angle, which is thought to be a major mechanism leading to PPKG. Also, the stromal bed left behind the Descemet’s membrane should theoretically be protective against drainage angle distortion. Although it is associated with a lower incidence of increased IOP as compared to PK, yet it is a significant (0-18%).

**Mechanisms of glaucoma**

**Early postoperative period**

- Pre-existing open angle glaucoma / peripheral anterior synechiae (Figure 1)
- Inflammation
- Hyphaema

### Risk Factors

<table>
<thead>
<tr>
<th>Pre-operative</th>
<th>Intra-operative</th>
<th>Post-operative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age more than 60 years</td>
<td>Tight suturing</td>
<td>Development of fine or broad based PAS</td>
</tr>
<tr>
<td>Preexisting glaucoma</td>
<td>Larger trephine sizes</td>
<td>Significant angle damage due to development of PAS or severe intraocular inflammation</td>
</tr>
<tr>
<td>Aphakia</td>
<td>Long bites of individual sutures</td>
<td>Post operative steroid use</td>
</tr>
<tr>
<td>Preoperative diagnosis of:</td>
<td>Increased peripheral corneal thickness</td>
<td></td>
</tr>
<tr>
<td>✓ Adherent leukemia</td>
<td>Graft host disparity (donor size smaller than host)</td>
<td></td>
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<tr>
<td>✓ Bullous keratopathy</td>
<td></td>
<td></td>
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<tr>
<td>✓ Herpetic keratitis</td>
<td></td>
<td></td>
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<tr>
<td>✓ Trauma</td>
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<tr>
<td>✓ Perforated corneal ulcer</td>
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<tr>
<td>✓ Graft rejection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>✓ Mesodermal dysgenesis</td>
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</tbody>
</table>

Keratoplasty performed for keratoconus and corneal dystrophies are associated with a significantly lower risk of post-PK glaucoma.

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Glaucoma

- Pupillary block
- Retained viscoelastic material
- Blockage of peripheral iridectomy in case of an infected etiology
- Compression of the anterior chamber angle
- Collapse of the trabecular meshwork:

  Zimmerman et al proposed that mechanical collapse of the trabecular meshwork in aphakic grafts is responsible for the higher incidence of secondary glaucoma. They postulated that ciliary body-lens support system lends posterior support is afforded by the Descemet’s membrane. In aphakia, the posterior support is relaxed with the removal of the lens while anterior support is relaxed post PK after Descemet’s excision which leads to a partial trabecular collapse and obstruction of aqueous outflow.

**Late postoperative period**
- Progressive synechial closure
- Steroid induced
- Pupillary block
- Rejection/ inflammation sequelae

**Diagnosis**

**IOP measurements**
- In the early postoperative period, when the corneal surface is irregular, IOP can measured using
  - Mackay-Marg electronic applanation tonometer
  - Pneumatic applanation tonometer
  - Tono-pen
  - Dynamic contour tonometer (DCT)
- Goldmann applanation can be used to measure the IOP if the graft surface is smooth with an intact epithelium.
- Corneal epithelial edema and stromal edema predispose to inaccurately low readings, whereas corneal scarring will cause falsely high recording.

**Optic disc evaluation**

On every follow up with imaging at first examination and then subsequently at least once a year is recommended to detect any progression of glaucomatous optic neuropathy.

**Visual field testing**

May be difficult to perform in patients with a corneal graft, especially in the early postoperative period.

**Gonioscopy**

Provides assessment of peripheral anterior synechiae in the post operative period but is impossible in case of a failed graft where corneal edema precludes the visualization of anterior segment structures (Figure 2).

**Ultrasound biomicroscopy (UBM)**

Used to assess the angle and establish the cause for post-PK glaucoma, especially in eyes with a failed graft where anterior segment details are not clearly visible. The extent of irido-corneal adhesions, phakic/aphakic status, location of intraocular lens (IOL), anterior chamber (AC) depth, angle width and corneal thickness can be determined using UBM. In a UBM study done in eyes with post keratoplasty glaucoma, UBM showed the actual site of synechiae, viz. peripheral anterior synechiae, synechiae at the graft host
junction, host junction synechiae, central irido-corneal synechiae and intraocular lens iris synechiae\(^9\) (Figure 3). It was thus concluded that UBM, serves as a useful tool for anterior segment evaluation in such cases and can help in planning the site for glaucoma filtering surgeries and drainage devices.

**Anterior segment OCT**

As compared to UBM, AS-OCT requires no contact or immersion for evaluation of the depth of the anterior chamber angle and the causes of secondary angle closure\(^10\) (Figure 4).

**Management**

**Preventive Measures**

- Prior to keratoplasty

Pre-existing glaucoma should be appropriately managed either medically or surgically

- During keratoplasty
  - use of an oversized donor button (0.5 mm)
  - deep, short and equal bites
  - goniosynechialysis in the presence of peripheral anterior synechiae
  - iridoplasty in cases of floppy iris
  - removal of viscoelastic material at the end of the procedure
  - careful wound closure to prevent postoperative wound leaks

- In the postoperative phase
  - optimum use of steroids
  - use of cycloplegics to keep the pupil mobile and prevent pupillary block glaucoma

**Medical management**

- Medical control of IOP is the first line of treatment for post keratoplasty glaucoma.
- Currently available medications include:
  - Beta-adrenergic blocking agents (timolol, betaxolol)
  - Alpha-2-adrenergic agonists (brimonidine, apraclonidine hydrochloride)
  - Miotics (pilocarpine, echothiopate iodide, and carbachol)
  - Prostaglandin analogues (latanoprost, bimatoprost and travoprost)
  - Adrenergic agents (epinephrine & dipivefrin) are rarely used in current practice, as they are not very effective and cause chronic conjunctival inflammation.
- Miotics have little effect in the presence of angle closure caused by PAS and no longer recommended. They also promote breakdown of blood aqueous barrier, stimulating graft rejection and increasing the risk of retinal detachment, particularly in aphakes.
- Topical carbonic anhydrase inhibitors (dorzolamide and brinzolamide) suppress carbonic anhydrase enzyme in the corneal endothelium and long-term
Possible disadvantages of the various anti-glaucoma medications in patients with post-keratoplasty glaucoma

<table>
<thead>
<tr>
<th>Anti-glaucoma medication</th>
<th>Potential Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-Blockers</td>
<td>SPK, corneal anesthesia, dry eyes.</td>
</tr>
<tr>
<td>Alpha adrenergic drugs</td>
<td>SPK, dry eyes, allergic reactions.</td>
</tr>
<tr>
<td>Miotics</td>
<td>Inflammation, graft rejection, retinal detachment</td>
</tr>
<tr>
<td>Topical Carbonic anhydrase inhibitors</td>
<td>Altered taste, permanent graft failure in eyes with borderline endothelial counts.</td>
</tr>
<tr>
<td>Systemic Carbonic anhydrase inhibitors</td>
<td>Nausea, gastrointestinal disturbances, paresthesias, tinnitus, fatigue, depression, anorexia, weight loss, nephrolithiasis, and blood dyscrasias.</td>
</tr>
<tr>
<td>Prostaglandin analogues</td>
<td>Uveitis, cystoid macular edema in aphakia and pseudophakia and recurrent herpes simplex infection in patients with previous history of herpes.</td>
</tr>
</tbody>
</table>

Benzalkonium chloride, the preservative in most topical glaucoma medications, is toxic to the corneal epithelium.

use can lead to graft decompensation especially in presence of borderline corneal endothelial status.

**Surgical Management**

**Laser trabeculoplasty**

**Argon laser trabeculoplasty**

**Indications**

- Patients with open angles
- Clear grafts and
- Moderately elevated IOP (20-25 mmHg) on anti-glaucoma medications.

**Recommended settings**

50-µ spot size, 0.1-sec duration, and 600-900 mW of power.

**Complications**

Post-operative IOP spikes and uveitis, which can trigger graft rejection.

- Diode laser trabeculoplasty and selective laser trabeculoplasty may also be used.

**Laser iridotomy**

May be performed with an Nd:YAG (neodymium:yttrium-aluminium-garnet) laser, if a pupillary block is suspected.

**Trabeculectomy**

- In cases non-responsive to either medical therapy or ALT, trabeculectomy is advised.
- Conventional trabeculectomy is usually not effective, attributed to limbal conjunctival scarring from previous surgery, extensive peripheral synechiae, aphakia, and extremely shallow anterior chamber.
- Antimetabolites like 5-fluorouracil (5 mg of 5 FU in 0.1 cc is given daily as a subconjunctival injection for 7-10 days) and Mitomycin-C application (0.2-0.4 mg applied for 1-4 min subconjunctival or sub-scleral) has remarkably improved the success rate of filtering surgery for glaucoma.
- The reported success rate in IOP control with mitomycin trabeculectomy in patients with post-PK glaucoma is 67-91% and that of graft failure is 12-18%.

These agents appear to increase the success rate by inhibiting the fibroblast proliferation and enhancing the formation of filtering blebs.

- Glaucoma drainage devices (GDD).
- Offer an effective means for IOP control when filtering surgeries are less likely to be successful.
- Create alternate aqueous pathways by channeling aqueous humor from the anterior chamber through a long tube to an equatorial plate that promotes bleb formation (Figure 5).

- There are two types of GDDs, which can be used:
  1. Valved devices – offer resistance to outflow (Ahmed valve; Krupin implant)
  2. Valveless – offer no resistance to outflow (Molteno implant, Baerveldt implant).
- The advantages of the valved devices especially that of the Ahmed glaucoma valve, is the ease of insertion and low incidence of hypotony in the immediate post-operative phase. However, the Ahmed valve is associated with a high incidence of increased IOP-hypertensive phase (as much as 80%), 1-3 months after the procedure, which may need needling and 5-FU injections. Drainage devices with a larger surface area, such as the double-plate Molteno and Baerveldt implant, on the other hand, appear to exhibit a lesser incidence of the hypertensive phase and may achieve slightly lower IOPs in the long term.
- The overall success rate and other complications, including corneal decompensation, appear to be similar among all GDDs.
Complications

- **Graft failure**

A high incidence of graft failure (average 36.2%) is associated with the use of GDD’s.

The drainage tube may provide a conduit for retrograde passage of inflammatory cells into the AC thus increasing the risk of graft failure.

- Shallow AC with iris/tube graft endothelial touch - might accelerate the process leading to graft failure.

- Conjunctival erosion

- Prolonged hypotony

- Tube obstruction/failure/ tube plate extrusion

- Epithelial down growth

- Infection.

Cyclodestructive procedures

- Used as the surgical procedure of choice in difficult and advanced cases when medical or surgical interventions fail to control the IOP.

- Control the IOP by decreasing aqueous humor production by destroying part of the ciliary body.

- Cyclophotocoagulation (CPC), Diode laser cyclophotocoagulation (DLCP) using cryo, Neodymium: Yttrium-Aluminium-Garnet (Nd:YAG) laser or a semiconductor diode respectively are the various options available.

Complications include decrease in the Snellen visual acuity, graft failure, persistent hypotony, anterior uveitis, epithelial defects, severe pain, phthisis bulb, hyphema, hypotony, intractable pain, sympathetic ophthalmia, scleral thinning, and vitreous hemorrhage.

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**Transpupillary argon laser photoagulation**

Another modality that describes use of Goldmann three-mirror lens to ablate the ciliary processes one at a time. The laser is set at 50-100 μm spot size for a duration of 0.1-0.2 sec with a power of 1000 mW.

**Conclusion**

Post-penetrating keratoplasty glaucoma remains one of the leading causes of graft failure and visual loss. Knowledge of the risk factors such as pre-existing glaucoma, aphakia and previous PK may help to limit the occurrence of glaucoma and to increase the chances of success of PK. Timely diagnosis of PPKG along with aggressive and timely management remains the cornerstone for preserving optimal graft clarity and visual function following keratoplasty procedures.

**References**