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Abstract
Glaucoma is a neurodegenerative disorder that affects the optic nerve and the inner layers of the retina. Increased intraocular pressure is a major risk factor in the disease. Chronic elevation of intraocular pressure specifically induces the death of retinal ganglion cells. Recent advances have seen a surge of new ideas and technologies to aid in the detection, treatment and further understanding of glaucoma. These technologies and advances are discussed to provide information on risk-factors, diagnosis and treatment. This study reviews current concepts in the goals of glaucoma therapy, and options for the management of glaucoma.

Keywords: Glaucoma, optic nerve, Intra ocular pressure, retinal ganglion cell.

1. Introduction
Glaucoma, an optic neuropathy, is a worldwide leading cause of visual impairment and blindness. It is a progressive neurodegenerative disease of retinal ganglion cells associated with characteristic axon degeneration in the optic nerve. Elevated intraocular pressure (IOP) is the leading risk factor of glaucoma. Control of IOP with minimum complications is the first line treatment of glaucoma. Increased IOP are generally due to decreased outflow of aqueous humor [1-2]. It is estimated that about 60 million people is affected by glaucoma and it leads to bilateral blindness in 8.4 million people worldwide [3].

The aqueous humor is produced by cillary body; a tiny gland situated behind the iris constantly circulates through the anterior chamber. It flows through the iris and lens and flows out through a very tiny spongy tissue called trabecular mesh work, which acts as the drain of eye. When the trabecular meshwork becomes clogged, aqueous humor cannot leave eye and leads to fluid back up. The backed up fluid causes increased pressure within the eye [4].

1.1. Anatomy and Physiology of Eyes [5, 6]
The eyeball is the organ of sight. It is almost spherical in shape and has a diameter of about 2.5cm. The outer or fibrous coat comprises the sclera and the cornea. The middle or vascular coat consists of the choroid, the ciliary body and the iris. The inner or nervous coat is the retina. The oxygen and nutrients are transported to the non-vascular tissue by aqueous humor.

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1.2. Structure of the Eye ball

Sclera: sclera is commonly known as the white of the eyes. It is tough, opaque tissue that serves as the protective outer coat of the eyes. Six muscles connect around the eye and control the eye movements. The optic nerve is attached to the sclera.

Choroid layer

The choroid lies between the retina and sclera. It is composed of layers of blood vessels that nourish the back of the eye. The choroid connects with the ciliary body toward the front of the eye and is attached to edges of the optic nerve and back of the eyes. The biconvex lens is situated just behind the pupil. The chamber behind the lens is filled with the vitreous humor, occupying 80% of the eyeball. The anterior and posterior chambers are situated between the cornea and iris, and iris and lens, respectively and filled with aqueous humor. The arterial supply to the ciliary processes is derived from the major arterial circle of the iris fed primarily by the long posterior ciliary arteries. The ciliary circulation typically divides into three zones. The first zone is at the anterior base of the processes and consists of arterioles and capillaries that drain into a venular system separate from the other zones. This zone is the boundary between the non-fenestrated capillaries of the iris and the fenestrated capillaries of the ciliary processes. The fenestrations in the ciliary capillaries permit passage of protein into the stroma, which establishes an oncotic pressure that is important in aqueous humor production. The second zone also originates at the anterior base but extends more anteriorly into the processes and then drains into marginal venules running along the inner edge of the processes that coalesce into an efferent venous segment that travels posteriorly into the pars plana and the vortex veins. The third zone supplies the posterior portion of the major processes and the minor processes if present. The morphology of ciliary processes and their attendant vascularization varies among mammalian species though all share an anterior arterial source and posterior venous drainage. The ciliary body’s small size, inaccessible location and complex vascular organization make it difficult to study ciliary hemodynamic.

The cornea: The cornea is the transparent, dome shaped window covering the front of the eye. It is a powerful refracting surface providing 2/3rd of the eye’s focusing power. There are no blood vessels in the cornea, it’s normally clear and has a shining surface. The cornea is an optically transparent tissue that conveys images to the back of the eye.

The cornea is considered to be the main pathway for the permeation of drugs into the eye. It is composed of 5 layers.

- The Epithelium.
- The Bowman’s Membrane.
- The Stroma or Substantia Propria.
- Descemet’s Membrane.
- The Corneal Endothelium.

1. The Epithelium: It is the outer most layer of the cornea. It prevents the passage of the foreign material such as dust or water into the eyes and provides a smooth surface that absorbs oxygen and other nutrients in tears.

2. The Bowman’s Membrane: This is an acellular homogenous sheet, about 8-14µm thick. This is positioned between the basement membrane of the epithelium and the stroma.

3. The Stroma or Substantia Propria: It is located behind the epithelium; the stroma comprises about 90% of cornea. It consists primarily of water; layered protein fibers and cells that nourish it. The unique shape, arrangement, and spacing of the protein fibers are essential in producing the cornea’s light conducting transparency.

4. Descemet’s Membrane: This lies between the stroma and endothelium.

5. The Corneal Endothelium: This is a single layer of cells located between stroma and aqueous humor. The primary task of endothelium is to pump excess water out of the stroma. Without this pumping action, the stroma would swell with water, become hazy and ultimately opaque.

The conjunctiva: it is basically involved in the formation and maintenance of the pre-corneal tear film an in the protection of the eyes. It is thin, vascularised mucous membrane that lines in the posterior surface of the eyelids and outer regions of the cornea. The human conjunctiva is 2- 30 times more permeable to the drugs than the cornea and it has been proposed that loss by this route is a major path for drug clearance.

2. Types of Glaucoma [7, 8]

Glaucoma can be classified according to anterior chamber angle findings and the presence or absence of disease (states) causing elevated IOP and accompanying factors. Different types of glaucoma are identified, that is generally classified into open angle or angle closure glaucoma based on the width of the angle between the cornea and the iris.

2.1 Primary Glaucoma

2.1.1. Open angle glaucoma

a) Primary open angle glaucoma (chronic open angle glaucoma, chronic simple glaucoma)

b) Normal pressure glaucoma (low pressure glaucoma)

2.1.2. Angle-closure glaucoma

a) Acute

b) Sub-acute

c) Chronic

d) Plateau iris

2.1.3. Congenital Glaucoma

1. Primary congenital glaucoma

2. Glaucoma associated with other development ocular abnormalities

3. Glaucoma associated with extra ocular development abnormalities
2.2. Secondary Glaucoma

1. Pigmentary glaucoma
2. Exfoliation syndrome
3. Due to lens changes
4. Due to uveal tract changes
5. Iridocorneoendothelial (ICE) syndrome
6. Trauma
7. Postoperative
8. Neo vascular glaucoma
9. Raised episclera venous pressure
10. Steroid-induced glaucoma.

Secondary Glaucoma

It refers to any form of glaucoma in which an identifiable cause in the elevated intraocular pressure leading to nerve damage and vision loss.

Normal-tension Glaucoma

Normal tension glaucoma is related to decreased blood flow to the optic nerve. This may eventually cause neuronal damage. In addition, these eyes appear to be more susceptible to pressure related damage within the normal or high normal range, and therefore a pressure lower than normal is often necessary to prevent further visual loss.

Drug-induced Glaucoma

Various therapeutic classes of drugs, such as anti-cholinergic, adrenergic, or corticosteroid effects, have been implicated in inducing or worsening glaucoma. Medications affect open angle and closed angle glaucoma differently. Drugs that dilate the pupil, for instance, may precipitate an acute attack of angle closure glaucoma but usually do not produce harmful effects in those with open angle glaucoma. Dilation of the pupil in angle closure glaucoma may cause the peripheral iris to bulge forward, blocking the trabecular meshwork. The aqueous humor is prevented from reaching the outflow channels, which results in increased IOP. Because excessive resistance to outflow in open angle glaucoma is caused primarily by changes within the trabecular outflow channels, dilation of the pupil usually will not increase the intraocular pressure.

3. Etiology

Glaucoma causes optic nerve damage. A person’s risk of developing optic nerve damage is broadly classified into intraocular pressure dependant and intraocular pressure independent. The various initiating factors of optic nerve damage caused by glaucoma include genetic predisposition, physical changes, and systemic diseases etc. elevated intraocular pressure is the major risk factor in the development of glaucoma.

4. Pathophysiology

Glaucoma is a group of condition in which there is increased intraocular pressure due to impaired drainage of aqueous fluid through the sclera venous sinus in the angle between the iris and cornea in the anterior chamber. Raised intraocular pressure may damage the optic nerve by

- Mechanical compression of the axons
- Compression of the blood supply causing ischemia of the axons.

The pathogenesis of glaucoma can be explained by three major theories;

- Mechanical (IOP related damage)
- Vascular (Decreased blood supply to optic nerve head)
- Biochemical (Decrease in neurotrophic effect or increased levels of neuro toxins).

4.1 Stages of Pathogenesis

There are five stages in the pathogenesis of glaucoma

- A variety of initial events, causing
- Changes in aqueous outflow, resulting in
- Increased IOP, which leads to
- Optic nerve atrophy, and finally,
- Progressive loss of vision.
5. Signs and symptoms [9, 10]
- Eye Redness
- Nausea
- Sudden loss of sight
- Blurred vision
- Headache or severe eye pain.
- Intense pain
- Tender eye area
- Seeing halos or rainbow like rings around lights


7. Management of glaucoma [12]
Glaucoma therapy is aimed to prevent the further damage in the optic nerve. Before the initiation of the glaucoma management therapy, requires a case to case risk to benefit analysis. Each treatment has its own risk and benefits which must be discussed with the patients before initiating the therapy.
The various factors that should be included are
- Severity and type of glaucoma
- Patient compliance
- Affordability
- General health and life expectancy of the patient.

Goals of medical management for glaucoma
- To achieve target IOP and reduce IOP fluctuations with possible medications.
- To administer glaucoma medication which have the least side effect on the patient.
- To achieve this treatment at an affordable and sustainable cost for the patient.
- Monitor the structure and function of the optic nerve for further damage and adjust the target IOP to a lower level if deterioration occurs.
- To treat non- IOP dependant systemic factors which may contribute to the development and worsening of glaucomatous optic neuropathy.
- To educate and involve the patient and his family in the management of the disease process.

7.1. Medical Therapy
There are five classes of topical hypertensive medication. They are prostaglandins, β-blockers, selective (α-2) adrenergic agonists, carbonic anhydrase inhibitors (CAIs), and cholinergic agonist.

<table>
<thead>
<tr>
<th>Meditations</th>
<th>MECHANISM OF ACTION</th>
<th>Efficacy</th>
</tr>
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<tbody>
<tr>
<td>Prostaglandin analogues</td>
<td>Increases uveo scleral outflow by remodeling the extracellular matrix between the ciliary musculature</td>
<td>Most efficacious of all topical anti-glaucoma medications. Decreases IOP to about 30 to 35%</td>
</tr>
<tr>
<td>β - blockers</td>
<td>Act on β adrenergic receptor on the ciliary body and decrease aqueous production.</td>
<td>Decrease IOP from 25-30% from baseline. Efficacy decreases over a period of time.</td>
</tr>
<tr>
<td>α-adrenergic agonists:</td>
<td>Acts on alpha adrenergic receptors on ciliary vascular system to decrease aqueous production.</td>
<td>20-25% decrease in IOP from base line.</td>
</tr>
<tr>
<td>Cholinergic agonists</td>
<td>Increases trabecular outflow.</td>
<td>Decreases IOP by 20-25%</td>
</tr>
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7.2. Surgical Treatment [13]

Laser surgery
Laser surgery for open angle glaucoma generally refers to laser trabeculoplasty. Laser trabeculoplasty has been used in the management of open angle glaucoma’s for more than 20 years. Initially it was performed with the argon blue-green wavelength, the same effect is achieved using argon green diode, and a frequency-doubled Nd: YAG laser, known as selective laser trabeculoplasty. There are some advantages to laser trabeculoplasty when compared with medical treatment or incisional surgery. It does reduce IOP in most patients, there is no risk of bleeding or infection because it is relatively noninvasive, there is less dependence on patient compliance to provide IOP control, and the IOP becomes less susceptible to diurnal variation. Laser trabeculoplasty results in an IOP reduction of 20% to 30% in most patients. The poor long-term success may be because of progression of the disease with worsening IOP or structural changes in the trabecular meshwork over time, such as scarring and fusion of trabecular beams. Selective laser trabeculoplasty (SLT) is a frequency doubled Nd: YAG laser that delivers a brief duration (3nS), large spot (400 μm), relatively low-energy (approximately 0.75 mJ) spot to the trabecular beams. It reportedly targets pigmented trabecular meshwork cells, possibly stimulating them to divide and provide improved outflow through the trabecular meshwork.

Incisional surgery
Incisional surgery is indicated in cases in which sufficient reduction of IOP cannot be achieved by other therapeutic means such as medical treatment or laser treatment, cases in which other appropriate means of treatment cannot be used because of adverse effects or non-compliance, and cases in which it is thought that sufficient reduction of IOP cannot be achieved by other therapeutic means. The indication for surgery must be made for each individual patient based on a comprehensive assessment of type of glaucoma, stage of glaucoma, the patient’s disease awareness, compliance, and the patient’s social background.

Filtrating surgery
In this surgery, a small hole is made in the corneal limbus in order to create a new aqueous outflow pathway between the anterior chamber and subconjunctival space. The most serious complication is late infection of the filtering bleb. Patients
undergoing filtration surgery such as trabeculectomy should be given sufficient explanations concerning the risk of late infections.

(1) Full-thickness filtrating surgery
In this method, a direct aqueous outflow pathway from the anterior chamber is created underneath the conjunctiva. Compared to filtrating surgery in which a scleral flap is prepared, such as trabeculectomy, it is difficult to control filtration volume, and complications such as a shallow anterior chamber are frequent, so this technique is currently indicated only in a few extremely refractory cases.

(2) Trabeculectomy
In this procedure, a scleral flap is prepared, the limbal tissue is incised under the scleral flap, and the scleral flap is then sutured in order to regulate filtration volume. This is currently the most common type of glaucoma surgery. Although additional surgery and other treatments are required in some cases, long-term IOP control is achieved in most cases.

(3) Nonpenetrating trabeculectomy
In this technique, a portion of the tissue is incised underneath the scleral flap to form an aqueous outflow pathway without penetration of the anterior chamber. Compared to trabeculectomy, this procedure shows few early postoperative complications and to show high postoperative IOP.

(4) Implantation surgery
In this method, an aqueous outflow pathway is created between the anterior chamber and the outside of the eye using a special implant. This procedure is used in patients in trabeculectomy with antimetabolites is failed, patients with excessive conjunctival scarring due to previous ocular surgeries, patients with risk factors for a poor result with trabeculectomy, and patients in whom filtrating surgery is going to be technically difficult.

(5) Aqueous outflow pathway reconstruction surgery
a. Trabeculotomy
In this procedure, a trabeculotome is inserted into Schlemm's canal under the scleral flap and is rotated in the anterior chamber in order to incise the trabecular meshwork from outside so as to promote aqueous outflow via Schlemm's canal.

b. Goniosynechialysis
In this procedure, goniosynechiae in eyes with angle-closure glaucoma are lysed and aqueous outflow via the physiological pathway is promoted in order to reduce IOP. This procedure is more effective if carried out concurrently with cataract surgery.

c. Goniotomy
Under observation with a gonioscopic lens, a knife inserted via the cornea is used to incise the anterior chamber angle from the anterior chamber side. This procedure is indicated in developmental glaucoma

8. Concerns with generic ocular hypotensive medications

Generic medications have the same level of bioequivalence, because they are required to contain solubility and ocular penetration, and inactive ingredients may ultimately affect the drug’s effectiveness. Preservatives alone can influence a drug’s ability to penetrate into the eyes. Inactive ingredients include preservatives and adjusters of pH and tonicity. They can affect the bioavailability of the drug by interfering with its ocular permeability.

Alpha-2 Adrenergic Agonists
The first selective alpha-2 adrenergic agonist, brimonidine tartrate 0.2%, preserved with benzalkonium chloride. This agent was introduced to the US market in 1996. It has since been reformulated by reducing the concentration of the active ingredient, brimonidine tartrate, to 0.15%, and by replacing the preservative with Purite. The two drugs reduce IOP comparably.

Beta-Adrenergic Antagonists
Timolol maleate is a nonselective topical beta-blocker for treating ocular hypertension and glaucoma, and the agent is typically administered b.i.d. Timoptic XE 0.5% ophthalmic solution is a gel formulation of timolol maleate that was developed to enhance the drug’s delivery into the eye and to lower systemic absorption by providing a longer ocular contact time. The efficacy and safety of Timoptic XE 0.5% administered q.d. is similar to timolol maleate 0.5% solution used b.i.d.

Systemic carbonic anhydrase
Diamox is an oral CAI that is very effective at reducing IOP. The systemic administration of a CAI is usually reserved for patients with uncontrolled IOP who are on maximal tolerated topical medical therapy.

9. Conclusions
According to the World Health Organization (WHO), glaucoma is thought to be a leading cause of blindness worldwide, second only to cataracts. It presents the most significant public health challenge because it is irreversible. Treatment options for patients with glaucoma include medications, laser therapy, and incisional surgery. The risks and benefits of each type of treatment must be carefully considered to maximize the treatment’s benefits while minimizing adverse effects.

10. Acknowledgments
It gives immense pleasure in acknowledging with gratitude for the help, guidance and encouragement rendered to me by a host of people, to whom we owe a substantial measure for the successful completion of this review article. We take this pleasant opportunity to express our regards and gratitude to our dear parents, teachers and friends for their ever inspiring attitude.

11. References