

Study About the Ocular Drug Delivery System

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Abstract: By overcoming the particular anatomical and physiological barriers of the eye, the ocular drug delivery system is a specialist sector that aims to improve the treatment of eye illnesses. Due to quick tear drainage and inadequate medication penetration, conventional techniques like eye drops have poor bioavailability, which lowers their therapeutic efficacy. The structure of the eye, frequent ocular conditions such as cataract, glaucoma, dry eye disease, conjunctivitis, and eye stroke, as well as their pathogenesis and therapeutic methods, are the main topics of this project. The study underlines the necessity for sophisticated drug delivery methods and draws attention to the difficulties in delivering medications to both the anterior and posterior parts of the eye. Numerous contemporary methods, including sustained-release systems, in-situ gels, and nano formulations, have been proposed to increase drug retention, boost bioavailability, and lower dosing frequency. Furthermore, developments in therapeutic and surgical approaches are investigated, such as phacoemulsification, intraocular lenses, and laser-assisted procedures. In order to enhance patient compliance and therapeutic results in the treatment of ocular disorders, this project offers a thorough overview of ocular drug delivery methods, their drawbacks, and current advancements.

Keywords: Eye Disease, Eye Drops, Cataract, Glaucoma, Dry Eye Disease.

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I. INTRODUCTION OF OCULAR DRUG DELIVERY SYSTEM

Over the past three decades, there has been an increased focus on the prevalence of vision-related illnesses, mostly due to the global population's increased longevity. About 216 million had moderate-to-severe vision impairment, 188 million had minor vision impairment, and 40 million were legally blind ^[1]. These numbers are only expected to increase in the future. The eye is a complex vital system with a number of physiological and anatomical limitations. The cornea, conjunctiva, aqueous humor, iris, ciliary body, and lens are among the ocular tissues that make up the portion of the eye that is involved in refraction and vision, whereas the back portion of the eye is primarily composed of the vitreous humor and choroid. AMD, diabetic retinopathy (DR), CMV, vitreoretinopathy, and posterior uveitis are the conditions that most often influence the rear of the eye ^[4], whereas glaucoma, anterior uveitis, cataracts, and dry eye illnesses are common conditions that affect the front of the eye ^[2, 3]. The human eye is a unique organ made up of its physiologically autonomous activities due to its complicated anatomical and physiological structure. The development of medication delivery devices for it is further complicated by its diverse variety of structures ^[5]. The main issue with the traditional ocular medication delivery method using eye drops is their quick and significant medication loss due to considerable

excretion from the eye ^[6]. Only a tiny percentage of the medication in eye drops gets past the corneal layer and into the interior tissues of the eye ^[7]. The eye is a very delicate organ with a complicated physiology. This structure is composed of both anterior and posterior parts. Vision impairment generally significantly impacts the quality of life, originated from a range of diseases. Cataracts are the leading cause of blindness worldwide. Between 40 and 60 percent of blindness worldwide is caused by cataract complications^[8]. Early cataract development is caused by mutations in α , β , and γ crystallin and associated genes [9]. Glaucoma is a well-known optic neuropathy disorder that is associated with elevated intraocular pressure (IOP). It causes blindness that cannot be reversed. late in the procedure ^[10]. Vision impairment is also associated with age, diabetes, and fungal infections. These factors highlight the importance of regular eye examinations and proactive management of eye health, especially in at-risk populations. Advances in medical technology and treatment options are crucial for preventing vision loss and improving outcomes for those affected by these conditions.

II. ANATOMY OF EYE

The eyes of children and adults differ in many ways. From 2.3 to 3.4 g at birth to 7.5 g in adulthood, the weight of the eyeball almost doubles as a child grows. ^[11] The volume of a baby globe is between 2.20 and 3.25 cm³. ^[12] The

distance between the anterior surface of the cornea and an interference peak that symbolizes the retinal pigment epithelium (RPE)/Bruch's membrane is known as the AL.^[13] The AL of a newborn is normally 16.5 mm. The AL goes through three phases of transformation. The first phase, which spans from birth to two years, is characterized by rapid growth. Compared to newborns, AL is ten times higher in adults. Growth slows down in the third phase (5–13 years) following the second and third stages (2–5 years), and then the rate falls even further to roughly 0.4 mm/year.^[1] The increase in the AL dimensions differs in pathological diseases such as congenital glaucoma, congenital cataracts, and retinopathy of prematurity. AL monitoring is essential for controlling intraocular pressure in congenital glaucoma.

➤ *External Structures of the Eye*

- *Sclera:*

The sclera is the outermost layer of the eye and is also called the white of the eye. It is a robust, fibrous covering that provides protection and maintains the eye's shape. Furthermore, the sclera serves as an anchor for the eye's muscles.^[14]

- *Cornea:*

The transparent, dome-shaped structure in front of the eye is called the cornea. It is necessary to focus light onto the retina and act as a barrier against illnesses and other objects.

- *Conjunctiva:*

The sclera is covered by the conjunctiva, a thin, transparent membrane that borders the inside of the eyelids. It helps lubricate the eye and shields it from external irritants.^[15]

- *Eyelashes and Eyelids:*

The lashes act as a barrier against dust and debris, while the eyelids are movable skin folds that protect the eye. In order to keep the eye moist, tears are also distributed through the eyelashes.

- *Tear Glands:*

Tears and accessory glands in the eyelids are produced by the lacrimal glands. They prevent dryness and maintain optical clarity by lubricating and nourishing the surface of the eye.

➤ *Middle Structures of the Eye*

- *Iris:*

The coloured part of the eye is called the iris. It controls the size of the pupil, which in turn regulates the amount of light that enters the eye. Pigmented cells in the iris determine an individual's eye color.

- *Pupil:*

The black, central orifice of the iris is known as the pupil. In low light, it dilates to let in more light, while in strong light, it constricts to let in less light.^[16]

- *Lens:*

Light is accurately focused onto the retina by the crystalline lens, which is located behind the iris. The eye's flexibility allows it to focus on objects at various distances; this process is referred to as accommodation.

- *Retina:*

The main anatomical issue in pediatric retinal surgery is that the globe and orbit are smaller than those of an adult. The ciliary body of the eye is composed of the pars plicata, which is the same size as an adult in a mature infant, and the pars plana ciliaris, which is relatively smaller in a mature newborn than in an adult. The pars plicata route is employed for vitrectomy in neonates; however, one of the main limitations that leads to limited changes is its proximity to the lens. Scleral buckling after retinal detachment procedures results in an adult refractive error of about -2.75D. However, this anisomyopia may be more acute in children's eyes due to the axial elongation caused by the surrounding band.^[17]

- *Orbital Structure:*

There seems to be a biphasic pattern to orbit formation.^[18]

The development of the orbital bones is especially crucial during the first three years of life. [19] During the second phase, orbital expansion is closely related to the sinus pneumatization process. [20]

- *Aqueous Humor:*

Aqueous humor, a jelly-like substance found in the outer/front chamber of the eye, fills the "anterior chamber of the eye," which is located just beneath the cornea and in front of the lens. Aqueous humor is a salt solution that is very slightly alkaline and contains trace amounts of sodium and chloride ions. It is constantly produced, primarily by the ciliary processes, and travels from the posterior chamber into the anterior chamber via the pupil before leaving through the uveoscleral and trabecular routes at the angle. The circular Schlemm's canal is also referred to as the scleral venous sinus or the anterior ciliary veins. It is located at the junction of the cornea and sclera. Human aqueous humor turnover occurs at a rate of 1% to 1.5% of the anterior chamber volume each minute. The rate of aqueous production is around 2.5 µl/min. In aqueous humor, there are both pressure-dependent and pressure-independent pathways.

- *Macula:*

The region in the center of the retina is called the macula. The macula has a large concentration of photoreceptor cells, which convert light into nerve signals. The macula's high concentration of photoreceptors allows us to see small details like newsprint. At the very center of the macula lies the fovea, where our sharpest vision takes place.

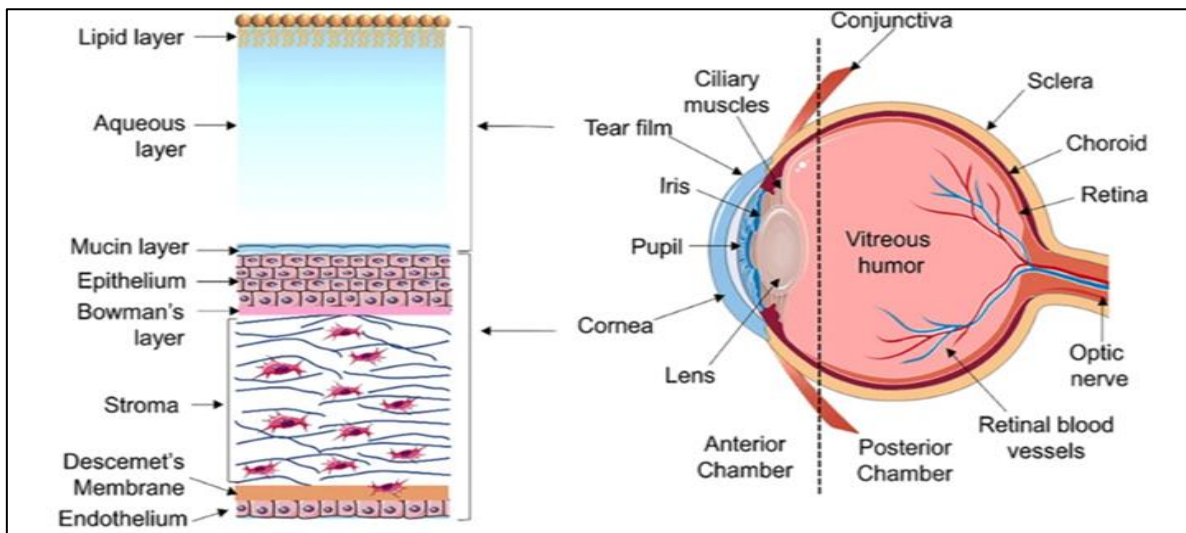


Fig 1 Anatomy of Eye [21]

III. VARIOUS OCULAR DISEASE

A. Cataract

Cataracts are the most common cause of visual loss worldwide. Between 40 and 60 percent of blindness worldwide is caused by cataract complications [22]. Risk factors include smoking, genetic determinism, diabetes, poor nutrition, and exposure to UV radiation. The three forms of cataracts are cortical, nuclear, and posterior subcapsular [23]. Lens transparency is regulated by the crystallin protein [24]. However, using anti-cataract drugs early on may lessen the need for surgery. Anti-cataract drugs are multifunctional antioxidants with the ability to bind and hunt radicals [25]. Anti-cataract drugs include curcumin, lanosterol, metformin, and resveratrol [26]. An emmetropic condition is often attained by the age of nine, but it can sometimes happen later. This is a crucial period for anatomical and physiological development [27]

As the lens flattens throughout the first two years, the power drops by 8 D. After that, it drops by an additional 11.5 D, reaching an adult value between the ages of seven and ten. Determining the precise strength of a child's eye is challenging since the visual system is so dynamic before the age of 10. The intraocular lens (IOL) power calculation in children is influenced by a number of factors, including the age at which the cataract develops, visual acuity at the time of presentation, the stage of cataract formation (congenital or developmental), the involvement of one or both eyes, and the refractive state of the opposing eye. [28]

➤ The Pathogenesis of Cataract Disease

A membrane structure known as the lens capsule encloses the transparent lens, which is composed of fibers (modified epithelial cells). There are two primary components to lens matter:

- The superficial cortex, which has younger fibers
- The deeper region of the nucleus, which contains older fibers

Loss of transparency and the eventual development of cataracts are caused by a variety of degenerative processes that denature and coagulate lens proteins found in lens fibers through several mechanisms. [29]

Disorders that arise at any stage of lens development (congenital cataract)

- Subcapsular cataract, or fibrous metaplasia of the lens epithelium
- Cortical hydration (cortical cataract) between lens fibers
- The accumulation of certain pigments, such as urochrome (nuclear cataract) [30]

All of these procedures eventually result in an opaque lens behind the pupil, which makes it very challenging for the patient to do daily tasks.

➤ Conventional Treatment of Cataract Disease

• Cataract Surgery:

In the developed world, cataract surgery is the most common surgical procedure. In developing countries, cataracts are the most frequent cause of blindness. In 1990, cataracts accounted for 40% of the estimated 37 million blind persons globally. Every year, an extra 1-2 million individuals go blind. Every five seconds, one person worldwide loses their vision, and a child does so every minute. Of these individuals, 75% had blindness that might be cured. [31]

➤ Treatment of General Disorders Prior to Surgery

For optimal outcomes, many general health problems need to be optimized prior to surgery. [32]

- Diabetes mellitus
- ✓ High blood pressure
- Myocardial infarction

- ✓ Angina
- ✓ Infection of the respiratory system
- ✓ A stroke
- ✓ A leg ulcer

- Hepatitis caused by viruses

- ✓ AIDS
- ✓ Epilepsy

- Parkinson's disease
- Rheumatoid arthritis

➤ *The Most Cutting-Edge Methods for Treating Cataracts are the Following:*

- *Femtosecond Laser-Assisted Cataract Surgery, or FLACS:*

FLACS is a laser procedure that allows surgeons to make precise incisions and break up clouded lenses (cataracts). It increases the accuracy of many surgical treatments, leading to better visual outcomes and a quicker recovery time.

- *Phacoemulsification:*

The fuzzy lens is broken up by ultrasonic energy and then suctioned out through a small incision. This method allows for fewer incisions, a quick recovery, and reduced eye strain.

- *IOLs (Advanced Intraocular Lenses):*

These advanced intraocular lens developments have altered cataract surgery. Astigmatism and presbyopia can be treated with the toric and multifocal lenses, which also allow for personalized vision correction. After surgery, it reduces the need for glasses and contact lenses.^[33]

➤ *Benefits of Contemporary Cataract Therapy Methods*

- Better results and accuracy with femtosecond laser technology
- Tailored intraocular lenses for individualized eyesight
- Fast and Minimal Invasive Techniques
- Quick Recuperation
- Enhanced Security and Decreased Issues
- Economical and Long-Term Solutions^[33]

B. Dry Eye Disease

Four out of fifty-four dry eye illnesses, which include symptoms including ocular surface irritation and visual impairment, are caused by either insufficient tear production or tear hyperosmolarity^[34]. Therefore, dry eye symptoms could be classified as insufficient or evaporative disorders^[35]. Consequently, the ocular surface gets inflamed, and the osmolality of the tear film rises^[36]. Dry eye disorders are thought to affect 5–30% of people over 50^[37–38].

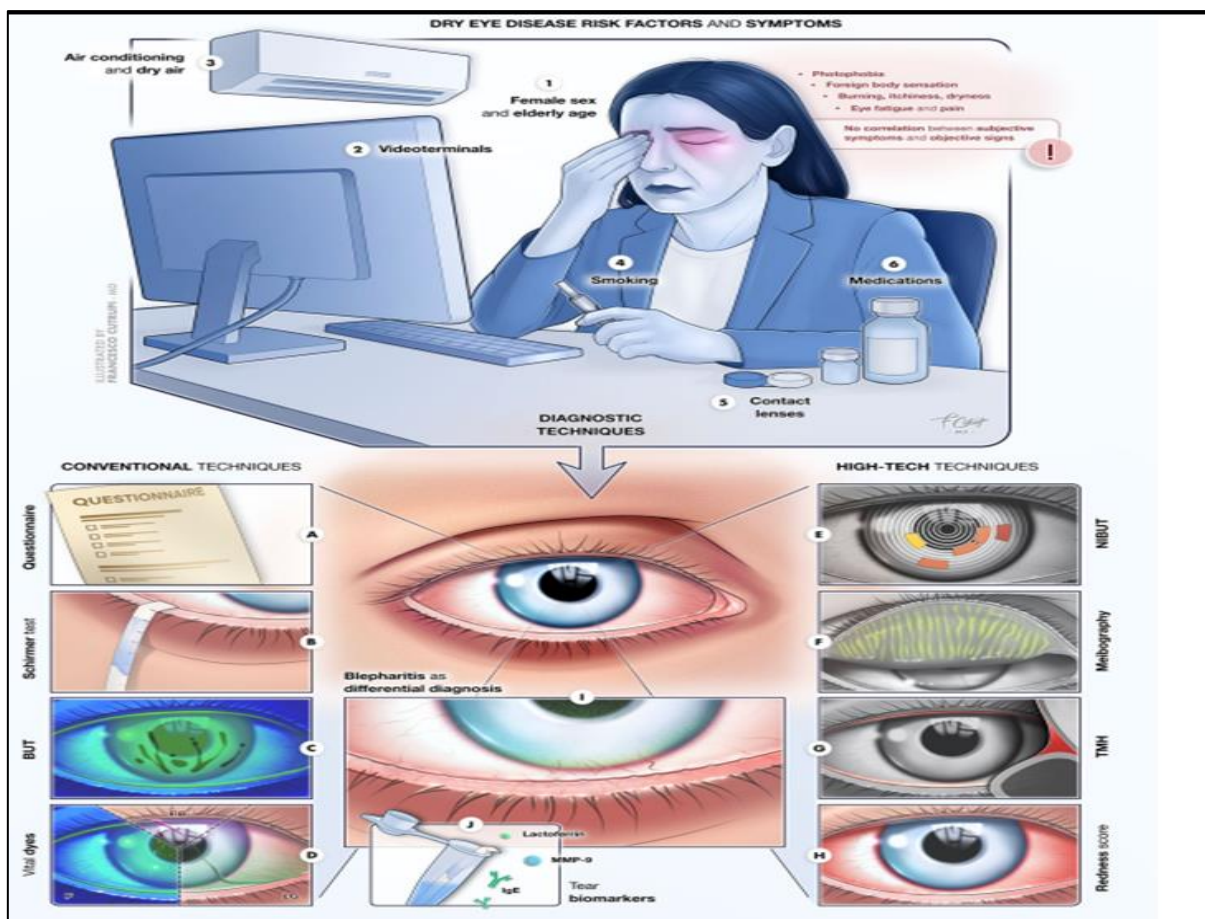


Fig 2 The Primary Pathophysiological Factors that Lead to the Development of Dry Eye Conditions.⁽³⁹⁾

➤ Pathophysiology of Dry Eye Disease:

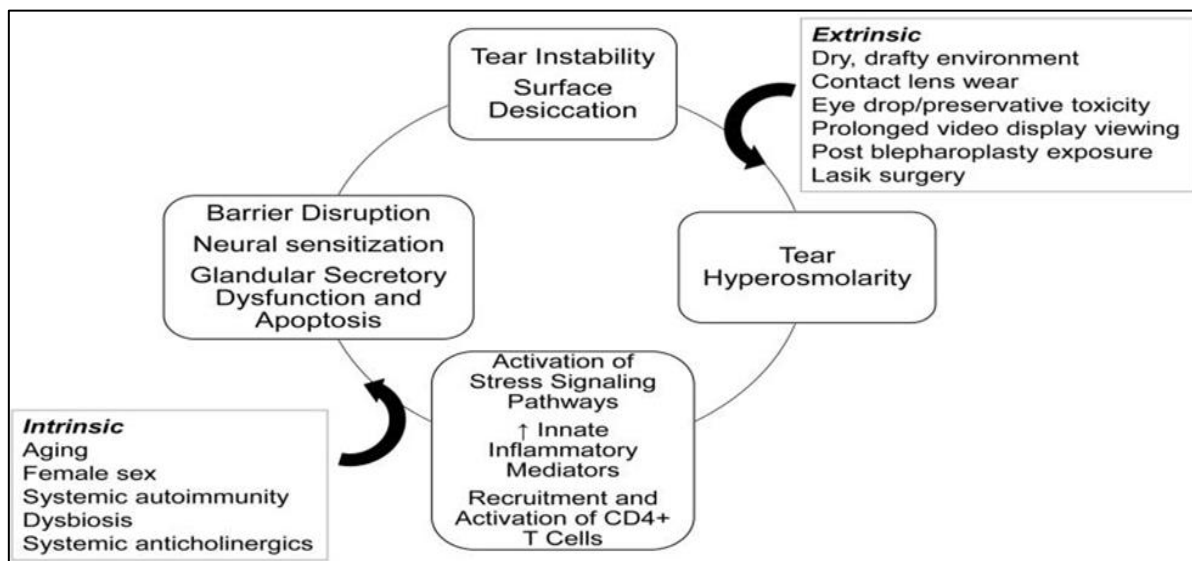


Fig 3 The Primary Pathophysiological Factors Contributing to the Development of Dry Eye Conditions. (40-46)

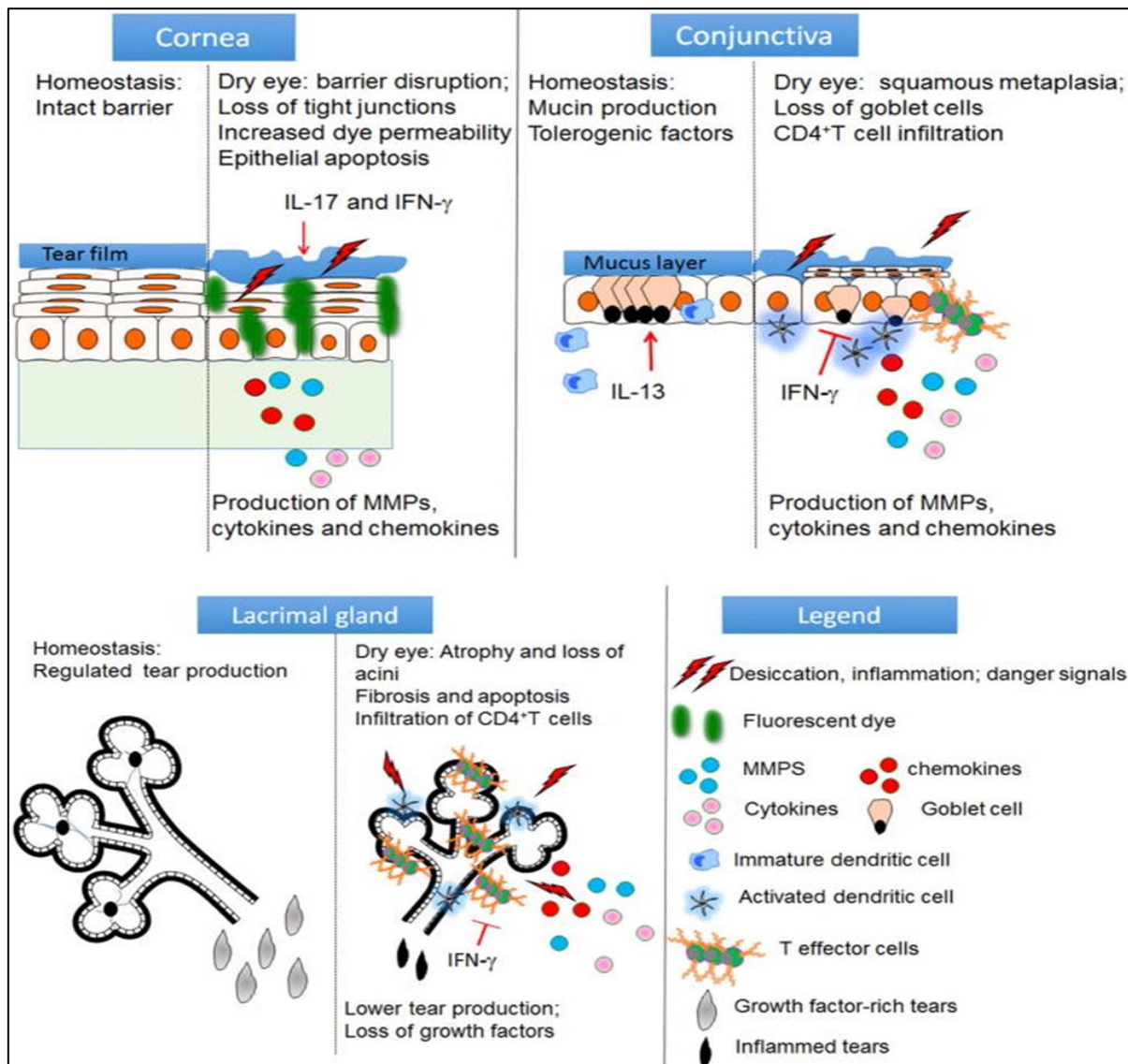


Fig 4 Dry Eye: An Inflammatory Condition that is Complex and Self-Sustaining (41-46)

➤ *Treatment of Dry Eye Disease:*

Patient education is essential and should address things like understanding that dry eye is a chronic condition and that medication is long-term and may not yield immediate effects. The step-ladder method to treating dry eye illness, which is based on the severity of the problem, must take into account meibomian gland dysfunction, (subclinical) ocular surface inflammation, and/or concomitant systemic disease. [47]

➤ *Artificial Tears:*

Artificial tears are the mainstay of treatment for all levels of dry eye severity. No comprehensive, randomized, controlled trials have been carried out to evaluate the vast array of artificial tears available on the market, despite the fact that artificial tears are regarded as standard. Artificial tears, most of which are marketed as CE items, are not licensed based on clinical efficacy. A few small randomized studies have shown that artificial tears

- Boost the stability of the tear film.
- Decrease the tension on the ocular surface
- Boost the surface's optical quality and contrast sensitivity
- Have the capacity to improve life quality [48-52]

➤ *Anti-Inflammatory Therapy:*

Even in cases of moderately severe dry eye, the ocular surface and lacrimal gland undergo an inflammatory response that is often asymptomatic (53-55). Anti-inflammatory drugs are necessary for patients with moderate to severe dry eye disease in order to break the vicious cycle of inflammation and surface degradation.

➤ *Eyelid Hygiene:*

The melting point of meibomian lipids is between 28 and 32°C. Meibomian gland dysfunction causes the melting point to rise to 35°C (e55). [56] The amount of lipid secreted depends on the temperature of the eyelid.

Table 1 Dry Eye Disease Treatment

Medication	Description	Mechanism of Action	References
Artificial tears	Polyvinyl alcohol, povidone, hydroxypropyl guar, cellulose derivatives, and hyaluronic acid	Increase tear film stability. Reduce ocular surface stress. Improve contrast sensitivity and the optical quality of the topical surface.	(57-62)
Topical corticosteroids (loteprednol)	Unpreserved corticosteroid drops, instilled over a period of 2 to 4 weeks, improve the symptoms and clinical signs of moderate to severe dry eye disease.	Corticosteroids act by the induction of phospholipase A2 inhibitory proteins and inhibiting the release of arachidonic acid.	(63-65)
Cyclosporin A (CsA)	release of parasympathetic neurotransmitters. CsA eye drops 0.05% (Restasis) were approved for the topical treatment of dry eye by the FDA in 2002.	CsA is an immunosuppressant that inhibits the calcineurin–phosphatase pathway by complex formation with cyclophilin, and thus reduces the transcription of T-cell-activating cytokines such as interleukin-2 (IL-2).	(66-70)
Tacrolimus / Pimecrolimus	Appear to be as effective as CsA and is used in patients who cannot tolerate CsA	Inhibition of interleukin-2 gene transcription, nitric oxide synthase activation, cell degranulation, and apoptosis.	(71)
Tetracyclines	Bacteriostatic antibiotics with anti-inflammatory effects.	They reduce the synthesis and activity of matrix metalloproteinases, the production of interleukin-1 (IL-1) and tumor necrosis factor, collagenase activity, and B-cell activation.	(72,73,74)

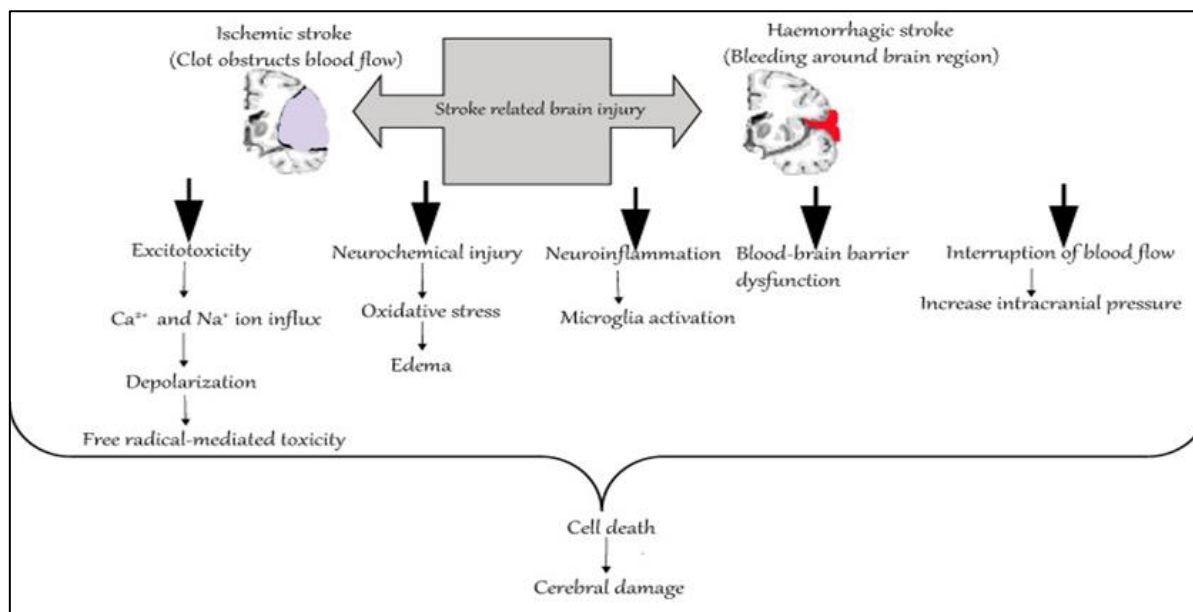
C. *Eye Stroke*

Blood artery blockage is a hallmark of the neurological disorder known as a stroke. Clots that form in the brain obstruct arteries and rupture blood vessels, disrupting blood flow and resulting in hemorrhage. When the arteries supplying the brain burst during a stroke, brain cells suddenly die from a lack of oxygen. (75)

➤ *Pathophysiology of Eye Stroke:*

A stroke is an abrupt neurological eruption caused by inadequate blood vessel perfusion to the brain. An understanding of the neurovascular anatomy is necessary to study the clinical manifestation of a stroke. Blood flow to the brain is regulated by two internal carotids in the front and two vertebral arteries in the back (the circle of Willis).

While ischemic stroke is brought on by inadequate blood and oxygen flow to the brain, Hemorrhagic stroke is caused by bleeding or leaking blood vessels. Ischemic occlusions cause about 85% of stroke deaths; intracerebral hemorrhages cause the remaining deaths. Ischemic occlusion in the brain results in thrombotic and embolic conditions. In thrombosis, vascular constriction caused by vascular atherosclerosis impacts blood flow. Plaque buildup eventually narrows the vascular chamber and forms clots, which causes thrombotic stroke. An embolism in an embolic stroke is caused by a reduced blood flow to the brain region, which results in severe stress and early cell death (necrosis). Organelles expand and the plasma membrane is damaged after necrosis. (76)

Fig 6 Molecular Mechanism of Stroke⁽⁷⁷⁾

➤ *Eyes and Stroke: The Visual Aspects of Cerebrovascular Disease*

• *Conventional Treatment of Eye Stroke*

✓ *Acute Management (First 6 Hours):*

The primary goal is to restore blood flow.

▪ *Intravenous (IV) tPA:*

Considered for patients presenting within 4.5 hours to improve functional outcomes.

▪ *Intra-Arterial Thrombolysis (IAT):*

Specialized delivery of medicine directly into the ophthalmic artery.

▪ *Ocular Massage:*

Manual pressure applied to the eye to help dislodge the clot.

▪ *Paracentesis:*

A needle procedure to remove fluid from the eye, lowering intraocular pressure.

✓ *Subacute/Secondary Care:*

Focused on preventing future strokes and managing complications.

▪ *Management of Underlying Factors:*

Treatment of underlying risks like high blood pressure, diabetes, and high cholesterol.

▪ *Laser Treatment:*

Pan-retinal photocoagulation to manage neovascularization (new, abnormal blood vessels).⁽⁷⁸⁾

D. Conjunctivitis Diseases

Conjunctivitis is characterized by conjunctival tissue inflammation and swelling, blood vessel enlargement, ocular

discharge, and pain. Many people worldwide suffer from conjunctivitis, which is one of the most frequent causes of visits to general medical and ophthalmology clinics. Over 80% of cases of acute conjunctivitis are reportedly diagnosed by non-ophthalmologists, including internists, family physicians, paediatricians, and nurse practitioners.⁽⁷⁹⁾

➤ *Treatment*

The cornerstone of treatment for many types of allergies, including allergic conjunctivitis, is allergen avoidance. Artificial tears serve as a barrier, dilute different allergens, and remove numerous inflammatory mediators from the ocular surface. Oral antihistamines are commonly used by patients with allergic conjunctivitis to lessen their ocular symptoms. Second-generation antihistamines are preferred because they have fewer adverse systemic side effects.^[80] Unfortunately, dry eyes brought on by oral antihistamines might worsen the symptoms of allergic conjunctivitis.^[81]

Steroids should only be used carefully and in certain circumstances. Sadly, any form of corticosteroid therapy is associated with cataract formation and elevated intraocular pressure. If the condition is severe, topical and oral treatment in addition to supratarsal injections are sometimes required.^[82]

E. Glaucoma Disease

The progressive deterioration of retinal ganglion cells characterizes glaucoma, a class of visual neuropathies. These neurons, which have cell bodies in the inner retina and axons in the optic nerve, are a component of the central nervous system. Degeneration of these neurons results in visual loss and cupping, a characteristic feature of the optic disc.⁽¹⁴⁸⁾ The basic basis of glaucoma and the variables that lead to its progression are not well understood.⁽⁸³⁾

➤ Pathophysiology of Glaucoma

Table 4 Type of Glaucoma, their Treatment and Diagnosis

Glaucoma Kind	An Explanation	Risk Element	Diagnosis	Options for Treatment	Citation
Open-Angle Primary Glaucoma	The most prevalent type is marked by optic nerve injury and a progressive rise in IOP.	Age, family history, myopia, African descent	Visual field testing, OCT, and tonometry are used for diagnosis. tonometry	Medications, laser therapy, surgeon	(84)
Angle-Closure Glaucoma	The angle between the iris and cornea closes in a less frequent, acute form, obstructing drainage.	Asian ethnicity, hyperopia, family history	Gonioscopy, IOP measurement, slit lamp examination	Immediate medical/surgical intervention, laser iridotomy	(85)
NTG, or normal-tension glaucoma	Despite normal IOP levels, optic nerve injury still occurs.	Migraines, family history, and vascular dysregulation	Visual field testing, optic nerve imaging	Improved blood flow, neuroprotective drugs, and decreased IO	(86)

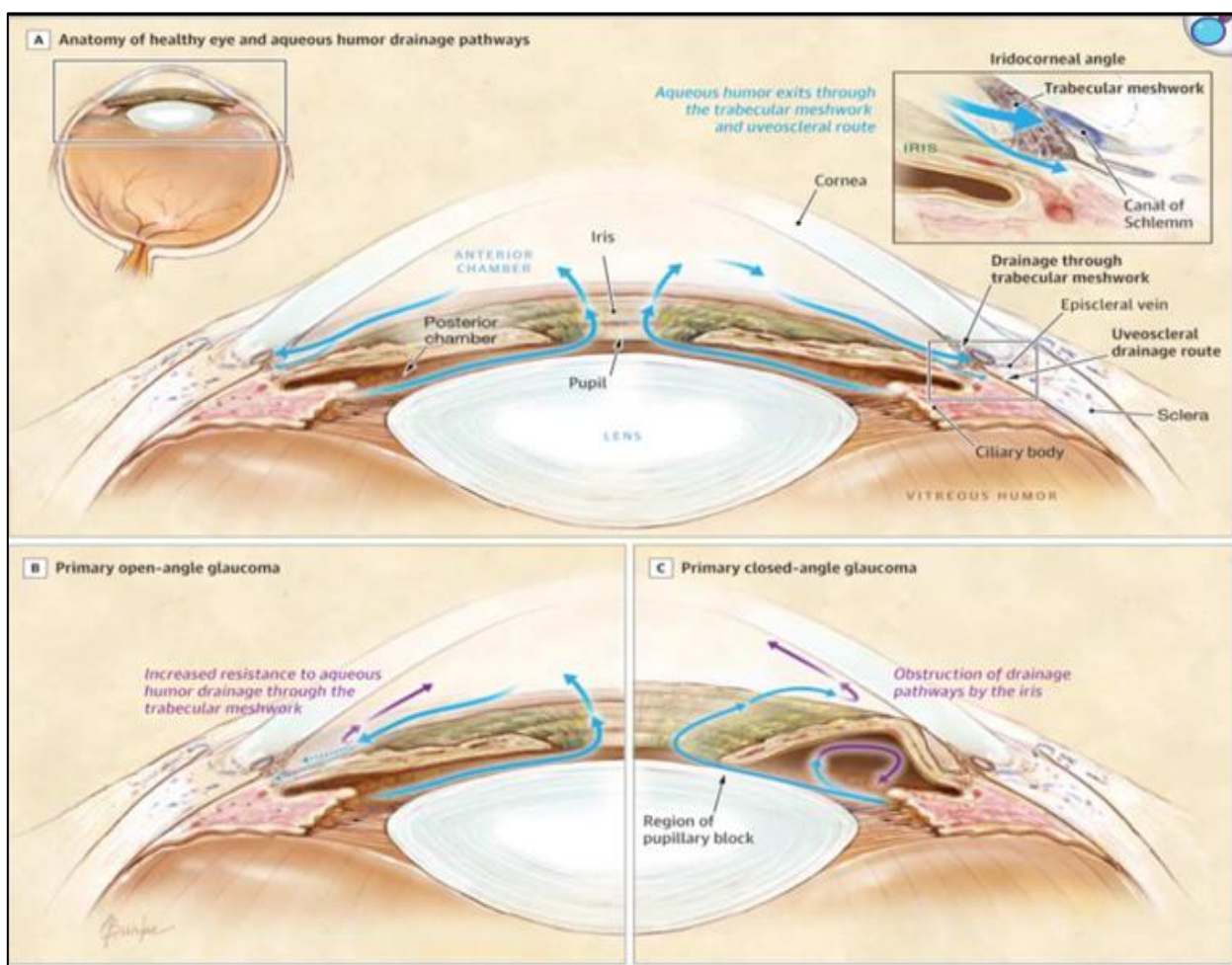


Fig 7 Pathways for the Drainage of Aqueous Humor in Healthy and Glaucomatous Eyes⁽⁸⁷⁾

IV. CONCLUSION

When treating a variety of eye conditions, ocular medication delivery systems are crucial. However, the eye has strong defensive barriers, such as tears, blinking, and restricted medication absorption, making it challenging to transport drugs to the eye. Because a significant amount of

medication is lost before it may start working, conventional techniques like eye drops and ointments are ineffective. Low bioavailability and frequent dosage are the results, which lower patient compliance. In this project, we examined the structure of the eye and learned how its physiology and anatomy impact drug delivery. We also go over common eye conditions like cataracts, glaucoma, dry eye disease,

conjunctivitis, eye stroke, and color blindness, as well as their causes, pathophysiology, and treatment, which mostly focuses on lowering intraocular pressure rather than treating the condition entirely. The study emphasizes that while traditional therapies are beneficial, they have drawbacks. For instance, glaucoma treatment mostly focuses on lowering intraocular pressure rather than treating the condition entirely, and cataract surgery is beneficial but requires appropriate maintenance. Similar to how conjunctivitis is treated based on its etiology (viral, bacterial, or allergic), dry eye illness necessitates long-term care. Modern methods have been developed to alleviate the drawbacks of conventional drug delivery. Nanoparticles, liposomes, in situ gels, and sustained-release formulations are examples of advanced drug delivery systems that enhance drug retention time, boost absorption, and offer controlled drug release. These devices increase patient compliance and decrease the frequency of medication delivery. Additionally, the safety and efficacy of managing eye diseases have been enhanced by innovative surgical methods and laser-based therapies. From basic eye drops to sophisticated and focused administration techniques, ocular medication delivery systems have generally made significant strides. These developments could improve patients' quality of life and lead to greater therapeutic results. Nonetheless, ongoing research is still required to create medication delivery methods that are safer, more efficient, and less expensive. Future developments will concentrate on enhancing medication targeting, minimizing adverse effects, and improving patient comfort during treatments. To sum up, better ocular drug delivery systems are crucial for managing eye conditions, and continued study will be crucial to this field's advancement.

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