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Emerging therapies in diabetic retinopathy: Focus on intraocular drug delivery

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Abstract
Diabetic retinopathy (DR), a prevalent microvascular complication of diabetes, is a leading cause of vision impairment and blindness worldwide. This condition is associated with type 1 and type 2 diabetes and is characterized by significant neurovascular damage in the retina. The underlying pathological mechanisms of DR involve neurodegeneration, inflammation, and oxidative stress. Current therapeutic approaches for DR, including anti-vascular endothelial growth factor (VEGF) therapy, corticosteroids, laser photocoagulation, and vitrectomy, have notable limitations. DR results from damage to the retinal blood vessels, leading to progressive vision loss in diabetic individuals. Intraocular drug delivery systems (IDDS) have emerged as a promising method for administering medications directly into the eye to manage DR effectively. Given the frequent need for intravitreal injections—typically on a monthly or bimonthly basis—to achieve therapeutic outcomes, recent research has concentrated on developing extended-release drug delivery systems. These advancements aim to reduce treatment frequency while maintaining efficacy. Strategies under clinical and preclinical evaluation include intravitreal implants, nanoparticles, hydrogels, combined systems, and port delivery devices, designed to ensure sustained drug release and improve patient outcomes.

Keywords: Diabetic retinopathy (DR), hyperglycemia, intraocular drug delivery, intravitreal injection, implants, nanoparticles

Introduction
Diabetic retinopathy (DR) is a major microvascular complication of diabetes mellitus (DM) and one of the primary causes of vision loss among the working-age population globally. Clinically, DR is characterized by pathological changes in the retina, including neovascularization, microaneurysm formation, protein exudates in the vitreous, and progressive decline in visual acuity [1, 2]. In developed countries, it is estimated that DR affects around 13 million individuals [3]. This condition emerges as a consequence of chronic hyperglycaemia, which disrupts normal vascular function and leads to retinal damage over time [4]. Diabetes mellitus, a chronic metabolic disorder resulting from genetic and environmental factors, is marked by sustained hyperglycaemia due to impaired insulin secretion, action, or both [5, 6]. In 2014, it was reported that over 422 million adults globally were living with diabetes, and projections indicate that this number will rise to 629 million by 2045, with low- and middle-income countries bearing the brunt of the burden [7, 8]. The inability to manage blood glucose effectively leads to a range of complications, categorized into macrovascular issues such as cardiovascular disease and microvascular complications, including retinopathy, nephropathy, and neuropathy [9]. Among the microvascular complications, DR remains particularly significant, affecting nearly all patients with type 1 diabetes and over 60% of individuals with type 2 diabetes within two decades of diagnosis [10]. The global burden of DR is staggering, with approximately one-third of all people with diabetes showing signs of retinal damage, including diabetic macular edema (DME) [11, 12]. In the United States, DR is a leading cause of blindness among adults, contributing to 12,000-24,000 new cases annually and accounting for a significant portion of the economic burden associated with diabetes care [13]. The pathophysiology of DR is complex, involving a combination of hypoxia, inflammation, and oxidative stress [14]. The condition progresses through distinct stages: non-proliferative DR (NPDR), characterized by retinal swelling and microaneurysms, and proliferative DR (PDR), where ischemic retinal tissue stimulates the

growth of abnormal blood vessels [15, 16]. Without timely intervention, PDR can lead to severe complications such as vitreous haemorrhage and tractional retinal detachment, culminating in vision loss [17].

Treatment modalities for DR, such as pan-retinal photocoagulation and anti-vascular endothelial growth factor (VEGF) therapies, have shown efficacy in slowing disease progression [18]. However, these approaches come with limitations. Laser photocoagulation, while effective, can cause collateral damage to retinal tissues, resulting in vision field loss [1]. Anti-VEGF therapies require frequent intravitreal injections due to their short intraocular half-life, imposing a significant burden on patients and healthcare systems [2]. Recent advancements in intraocular drug delivery systems (IDDS) offer promising alternatives for addressing these challenges [3, 4].

Innovations such as extended-release implants, nanoparticles, and hydrogels have been developed to provide sustained drug delivery, reducing the frequency of interventions while maintaining therapeutic efficacy [5, 6]. These emerging strategies not only enhance patient compliance but also alleviate the socioeconomic impact associated with frequent treatments [7].

This review aims to provide a comprehensive overview of the epidemiology, risk factors, pathophysiology, and current treatment strategies for DR, with a particular focus on advancements in pharmacological interventions and intraocular drug delivery systems [19-29]. Improved understanding of the mechanisms underlying DR and innovative therapeutic approaches can help mitigate the global burden of this vision-threatening condition.

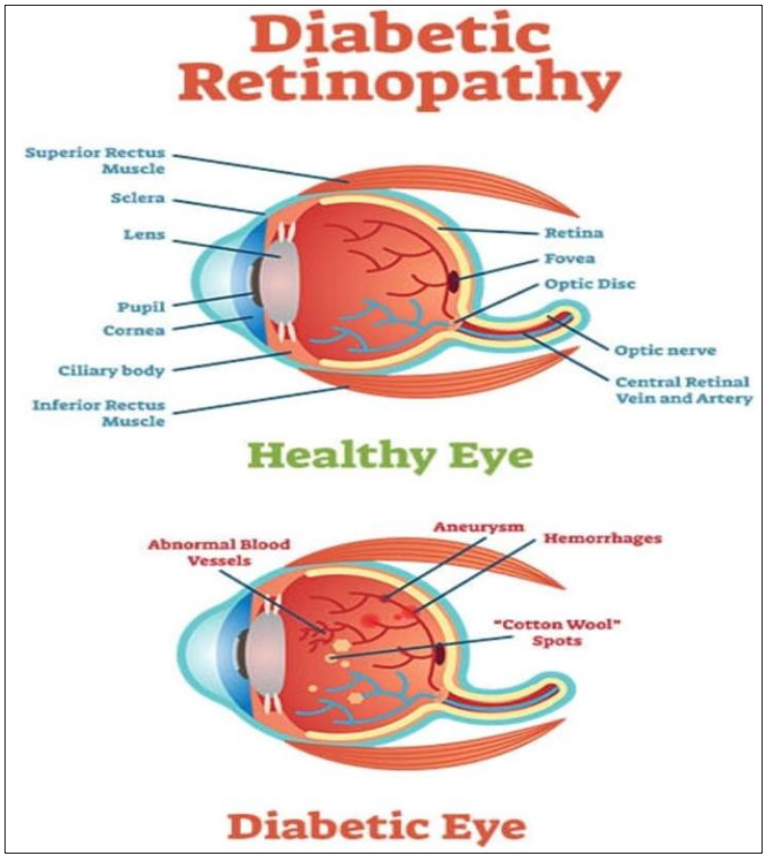

Fig 1: Healthy eye and diabetic eye

Vision-Related and Systemic Complications of Diabetes

Vision-Related Complications

Blindness: Advanced diabetic retinopathy (DR) can lead to severe vision loss or complete blindness.

Vision Impairment: Includes reduced visual acuity and blurred vision, often preceding blindness.

Ocular Complications

Macular Edema: Fluid accumulation in the macula, affecting central vision.

Glaucoma: Increased intraocular pressure that can damage the optic nerve and lead to vision loss.

Systemic Complications

Cardiovascular Disease: Elevated risk of heart attack, stroke, and peripheral artery disease.

Kidney Disease: Diabetic nephropathy, which can progress to kidney failure.

Neuropathy: Nerve damage, leading to pain, numbness, and weakness, particularly in extremities.

Diabetic Retinopathy: A Leading Cause of Vision Loss

Diabetic retinopathy (DR), a primary cause of vision deterioration, is driven by the vascular complications of diabetes. The condition arises due to leakage from the breakdown of the blood-retinal barrier and microvascular occlusion. DR is responsible for about 2.6% of global blindness and has significant prevalence among the working-age population (20-65 years). In South Asian countries, DR rates are lower (19.9%) compared to European countries (45.7%), with urban populations at higher risk due to dietary and lifestyle factors.

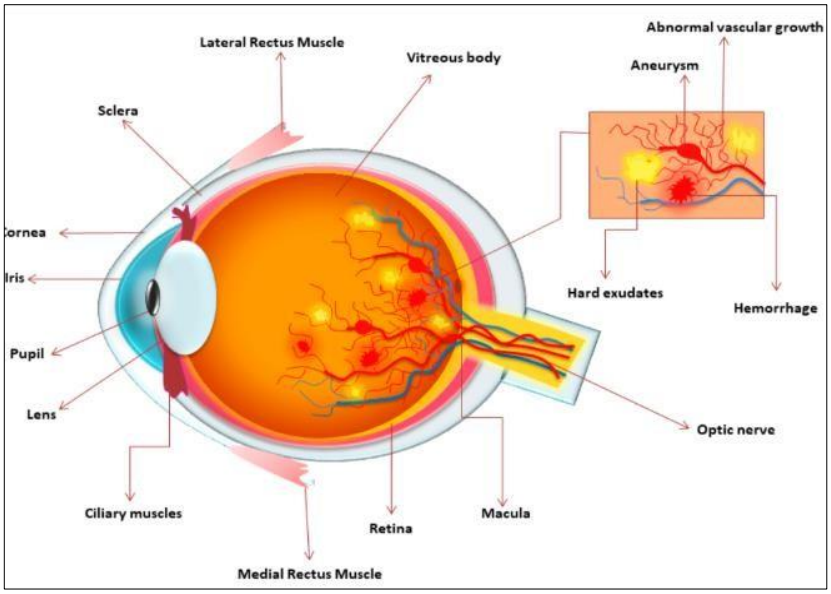

Fig 2: Diabetic Retinopathy Eye

Pathogenesis and Risk Factors of DR

DR typically progresses without symptoms, often remaining undetected until advanced stages when vision loss becomes irreversible. The exact mechanisms behind DR are not fully understood but are believed to involve factors like sleep apnea, histone modifications, DNA methylation, and non-coding RNA alterations. Risk factors for DR include hyperglycemia, hypertension, obesity, genetics, age, and sex. Regular blood glucose and blood pressure control, along with a healthy diet, are key to preventing or delaying DR onset.

Management and Pharmacological Interventions

Currently, there are multiple pharmacological options for managing DR. Anti-vascular endothelial growth factor (anti-VEGF) drugs, such as bevacizumab (Avastin), ranibizumab (Lucentis), and aflibercept (Eylea), are commonly used to inhibit VEGF, a critical mediator in the disease's progression. These treatments help control diabetic macular edema (DME) and retinal neovascularization but require frequent intravitreal injections due to the drugs' relatively short half-lives.

Anti-VEGF Therapy and Treatment Burden

Although effective, anti-VEGF therapies pose a significant treatment burden due to the need for regular injections and high healthcare costs. The therapeutic efficacy is achieved by blocking VEGF, which reduces vascular permeability and prevents further damage to retinal structures. However, frequent treatments make it challenging for patients and healthcare systems alike.

Vascular Endothelial Growth Factor (VEGF) and DR Pathogenesis

VEGF plays a crucial role in DR, contributing to the abnormal growth of blood vessels and increased permeability, which leads to complications such as macular edema, vitreous hemorrhage, and tractional retinal detachment. The isoform VEGF-A is particularly significant in DR's development.

Current Pharmacological Treatments for DR

Table 1: The following table summarizes the key drugs used in DR management

Drug	Dosage Form	Mechanism	Drug Delivery System
Triamcinolone acetonide	4 mg/0.1 mL (injection)	Anti-inflammatory	Intravitreal
Fluocinolone acetonide	0.59 mg (implant)	Anti-inflammatory	Intravitreal implant
Dexamethasone	0.7 mg (implant)	Anti-inflammatory	Extended-release implant
Bevacizumab	1.25 mg/0.05 mL (injection)	VEGF inhibitors	Intravitreal
Ranibizumab	0.5 mg/0.05 mL (injection)	VEGF inhibitors	Intravitreal
Pegaptanib	0.3 mg/0.09 mL (injection)	VEGF inhibitors	Intravitreal
Ruboxistaurin	32 mg/day	Inhibitor	Oral
Hyaluronidase	75 IU/0.05 mL saline	Vitreous hemorrhage clearance	Intravitreal

Ocular Drug Delivery Systems

Ocular drug delivery has seen advancements in achieving sustained drug release and improving treatment outcomes. Strategies such as tissue engineering, hydrogels, and nanoparticles are being explored to prolong the efficacy of intraocular drugs and reduce the need for frequent injections. These innovations aim to enhance drug delivery efficiency, increase biocompatibility, and provide better protection for biological drugs, thereby improving patient outcomes and reducing treatment burdens.

Drug Delivery Systems for DR Treatment and Management

Challenges in Drug Delivery to the Posterior Eye Segment

Delivering drugs to the posterior segment of the eye, where DR affects the retina, is challenging due to the eye's complex anatomical barriers. Conventional drug delivery methods, such as topical applications, face issues related to low bioavailability and frequent invasive procedures, such

as intravitreal injections. To overcome these challenges, innovative drug delivery systems (DDS) are being developed to improve drug penetration, enhance retention time at the target site, and provide sustained release with reduced toxicity and improved efficacy.

Types of Drug Delivery Routes

Topical Delivery

Although effective for anterior segment diseases, topical treatments are generally inefficient for posterior segment conditions due to ocular barriers such as the cornea, conjunctiva, and blood-aqueous barrier. However, recent research has focused on improving topical formulations for retinal diseases, such as dexamethasone-cyclodextrin complexes and regorafenib for neovascular age-related macular degeneration (AMD).

Subconjunctival Route

This method involves injecting drugs into the space beneath the conjunctiva, which can deliver compounds to the posterior segment.

Supra-Choroidal and Subretinal Routes

These routes utilize microcannulas and microneedles to deliver drugs directly to the choroid or beneath the retina, offering more direct access to the affected area.

Intravitreal Injections

The most common route for delivering drugs to the posterior segment, these injections provide direct access to the vitreous humor, allowing for the highest bioavailability of medications, such as anti-VEGF agents.

Tissue Engineering for DR Management

Stem Cell Therapy

Stem cell-based therapies are being explored to treat DR by repairing retinal damage caused by prolonged hyperglycemia. Bone marrow-derived stem cells (BMSCs) and human pluripotent stem cells (hPSCs) show promise in animal models for their anti-apoptotic and anti-inflammatory effects. Additionally, 3D retinal sheets derived from stem cells are being investigated for transplantation to restore retinal function.

Angiogenesis and Vascular Regeneration

Tissue engineering approaches focus on promoting angiogenesis to repair ischemic retinal damage. Engineered biomaterials and cell-based therapies aim to restore blood flow and support retinal function, addressing the neurovascular degeneration characteristic of DR.

Gene Therapy Integration

Gene therapy, particularly using adeno-associated virus (AAV) vectors, complements tissue engineering by delivering genes that regulate inflammation, oxidative stress, and vascular growth. When combined with stem cell therapies, gene therapy has the potential to enhance therapeutic outcomes.

Pathophysiological Insights: Research into the mechanisms of DR, including inflammation, oxidative stress, and epigenetic changes, is crucial for developing more effective tissue-engineered solutions. This knowledge is expected to lead to targeted therapies that better address the disease's underlying causes

Anti-VEGF Therapy for DR

Introduction to Anti-VEGF Drugs

Anti-VEGF therapies, including ranibizumab and bevacizumab, are gaining popularity for treating DR. These drugs inhibit VEGF, a key factor in angiogenesis, and are administered via intravitreal injection. Ranibizumab, a smaller monoclonal antibody fragment, has been approved by the FDA for treating neovascular age-related macular degeneration (AMD) and is also effective in reducing retinal thickness and improving vision in diabetic macular edema (DME). Clinical trials have shown that ranibizumab improves visual acuity and reduces macular thickness in patients with DME compared to laser therapy.

Bevacizumab Use in DR

Bevacizumab, a full-length monoclonal antibody, is primarily approved for metastatic colon cancer but is used off-label for treating DR. It has proven effective in preventing neovascularization associated with proliferative diabetic retinopathy (PDR) and DME. Clinical studies have demonstrated that bevacizumab offers better outcomes than laser therapy in some patients.

Dosage Forms for Ocular Drug Delivery

Hydrogels in Ocular Drug Delivery Hydrogels (HGs) are gaining attention for their potential to provide long-term sustained release of therapeutic agents, extending injection intervals while reducing side effects and risks. HGs are three-dimensional networks made from hydrophilic polymers, capable of holding large amounts of water and drugs due to their hydrophilic nature. Their properties, including biodegradability, swelling degree, permeability, and viscoelasticity, can be tailored by adjusting polymer type, concentration, and cross-linking. This customization affects drug release profiles, enabling better control over ocular drug delivery.

Examples of Hydrogels

Temperature-sensitive HGs: These hydrogels undergo a sol-to-gel transition in response to temperature changes. Examples include PLGA-PEG-PLGA and Poloxamer-based hydrogels loaded with drugs like Bevacizumab and Dexamethasone acetate.

Shear-sensitive HGs: These gels transition from sol to gel with shear force, enhancing their stability during injection.

In-Situ Gelling Hydrogels

In-situ gelling hydrogels are liquids that undergo phase transitions in response to physiological stimuli (e.g., temperature, pH, or ion concentration), forming viscoelastic gels that prolong drug retention and provide sustained release. These gels improve ocular bioavailability and are widely used for both anterior and posterior segment diseases.

Temperature-responsive hydrogels

Made from polymers like Poly(N-isopropylacrylamide) (PNIPAAM), these hydrogels undergo gelation at body temperature, improving drug retention and permeation in ocular tissues.

Ion-responsive hydrogels: Gellan gum is a commonly used ion-sensitive polymer that undergoes gelation in the presence of cations in tear fluids, offering controlled release in ocular treatments.

Nanocarrier-Mediated Ocular Drug Delivery
Nanocarriers, typically ranging from 10 to 1000 nm in size, are used to overcome the anatomical barriers of the eye. They provide controlled, targeted drug delivery and enhance the bioavailability of therapeutic agents. Nanocarriers can be designed for topical or intravitreal delivery, depending on the drug's target area.
Nanocarriers include:

Liposomes, dendrimers, and micelles: These carriers enhance drug stability, permeate ocular tissues more effectively, and improve drug retention. Cationic nanocarriers, in particular, interact electrostatically with the negatively charged ocular surfaces, enhancing drug delivery to the anterior segment.

Polymer-based nanocarriers: These offer sustained release of drugs and may be used in combination with other delivery systems like gels or implants for prolonged therapeutic effects.

Nanoliposomes: Nanoliposomes are lipid-based carriers designed to encapsulate both hydrophilic and lipophilic drugs. These vesicles have several advantages, including enhanced ocular permeability, reduced toxicity, and improved tissue retention time. However, they face challenges such as stability and limited encapsulation capacity, particularly for lipophilic drugs. Surface modifications can improve their stability and targeting efficacy.

Implants in Ocular Drug Delivery: Ocular implants are designed for controlled, long-term drug release, reducing the need for frequent injections. These implants can be biodegradable or non-biodegradable, offering tailored therapeutic approaches.

Biodegradable Implants: Biodegradable implants, including those made from poly (lactic-co-glycolic acid) (PLGA) or polycaprolactone (PCL), degrade naturally in the body over time, releasing the drug as the implant breaks down. They can be used for chronic conditions requiring prolonged treatment without the need for surgical removal.

Matricial (monolithic) systems: release the drug as the polymer degrades.

Reservoir systems: Release the drug through a membrane that degrades more slowly.

Non-Biodegradable Implants: Non-biodegradable implants, such as the Iluvien® implant, are used for conditions like diabetic macular edema. These small implants release drugs like fluocinolone acetonide over a period of 2 to 3 years, reducing the need for repeated injections and improving patient compliance.
These implants are typically inserted into the vitreous without the need for extensive surgery, offering a promising solution for long-term ocular drug delivery.

Conclusion

Intraocular drug delivery systems have significantly advanced the treatment of Diabetic Retinopathy (DR), offering targeted, sustained, and efficient drug delivery directly to the retina. These innovations, including nanoparticles, liposomes, and sustained-release implants, are improving therapeutic outcomes by enhancing bioavailability, reducing systemic side effects, and increasing patient compliance. Additionally, emerging therapies such as gene therapy and stem cell-based approaches show promise for retinal regeneration, while personalized medicine strategies are leveraging biomarkers and advanced imaging techniques to optimize treatment for individual patients. As research continues, these evolving technologies will address current limitations and expand the range of effective treatment options, ultimately improving the management and prognosis of DR for patients worldwide.

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