Article title: Diabetic retinopathy treatments based on nanotechnology
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DOI: 10.14293/S2199-1006.1.SOR-.PPQOQ83.v2
Preprint first posted online: 09 November 2022
Keywords: Diabetes mellitus, diabetic retinopathy, novel therapies, nanotechnology, drug delivery

REVIEW

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Diabetic retinopathy treatments based on nanotechnology

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Abstract:

Diabetes is a metabolic disorder characterized by a high level of glucose in the blood. Diabetes is projected to affect 366 million people by 2030, and the prevalence of diabetic retinopathy (DR) is expected to rise accordingly. DR is a multifactorial late-stage manifestation in diabetic patients. This hyperglycemia is potentially the leading cause of retinal vascular disorder. With DR consuming roughly 40% of the total cost of diabetes care in the US, it translates to approximately $120 billion annually in economic burden, not only from direct disease management costs but also from lost worker productivity. Although some treatments are available, there is no treatment yet that could fully attenuate clinical progression to reverse damage to the retina. These shortcomings make it imperative to explore non-invasive, novel, and cost-effective routes

for treating DR since all the available techniques are invasive, expensive, and primarily associated with side effects. Specialized databases and Mesh (terms defined as keywords by the researchers) were consulted to search for information that gathered scientific evidence on the subject in the last decade. Some of the databases used were: National Center for Biotechnology Information (NCBI), ScienceDirect, Cochrane Library, SpringerLink, and Clinicaltrials, among others. This review focuses on the importance of developing non-invasive alternatives for the treatment of DR.

Keywords: diabetes *mellitus*, diabetic retinopathy, novel therapies, nanotechnology, drug delivery

Introduction

Diabetic retinopathy (DR) is a common microvascular complication of diabetes *mellitus* (DM) and the primary cause of vision impairment in people worldwide. [1] DR is a multifactorial late-stage manifestation in diabetic patients. This hyperglycemia is potentially the main cause of retinal vascular disorder. [2] The DR is characterized by signs of retinal ischemia (microaneurysms, hemorrhages, cotton wool spots, intraretinal microvascular abnormalities, venous caliber abnormalities, and neovascularization) and/or signs of increased retinal vascular permeability. [3] DR progression occurs through two stages: the early non-proliferative diabetic retinopathy (NPDR) stage and the advanced proliferative diabetic retinopathy (PDR) stage, which with diabetic macular edema (DME) are the major causes of severe visual impairment (Table 1). [4] Unfortunately, the DR is commonly detected only in advanced stages (PDR), with unfavorable forecasts even with the proper treatment.

Diabetes is a metabolic disorder characterized by high glucose levels in the blood, and it is projected to affect 366 million people by 2030. The DR is a common microvascular complication of diabetic patients and the leading cause of vision loss in the working-age population worldwide. [5,6] Recent estimates suggest that approximately 486 million people worldwide have diabetes and that roughly one-third demonstrate evidence of DR, including DME. [7,8] Furthermore, the DR consumes roughly 40% of the total cost of diabetes care in the US and Europe, which is approximately $120 billion annually in economic burden, not only from direct disease management costs but also from lost worker productivity. [9] These disturbing numbers make DR a significant global public health and economic issue. [10]

Table 1 Differences between non-proliferative diabetic retinopathy, proliferative diabetic retinopathy, and diabetic macular edema

Stage	Characterized by	Risk factors
NPDR	Increasing signs of retinal ischemia including hard exudates, microaneurysms, IRMAs, and multiple blot hemorrhages	Hyperglycemia, hypertension, diabetes duration, type 1 diabetes, pregnancy, and cataract surgery[2,11,12]
PDR	New vessels developing in DR are characterized according to whether they develop, such as NVDs and NVEs	
DME	Accumulation of exudative fluid at the macula, the highly sensitive area of the retina responsible for sharp central vision	DR, dyslipidemia, diabetes duration, and type 2 diabetes[13-15]

Notes: NVDs are defined as any new vessel developing at the optic disc, while NVEs are any new vessel developing more than one-disc diameter away from the edge of the optic disc.

Abbreviations: NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; DME, diabetic macular edema; IRMAs, intraretinal microvascular abnormalities; DR, diabetic retinopathy.

According to the American Diabetes Association, the recommended tool for preventing vision loss from DR is timely screening and identification of patients at risk. As control of blood glucose in patients with diabetes is essential to prevent progression and complications, regular examinations are also the means for timely application of treatment in the early stages. [16] The primary goal of treating DR is to prevent further damage and decrease the damage caused to the tissue due to chronic hyperglycemia. [17] The foremost surgical or pharmacological therapies for treating PDR and DME are intravitreal injections, laser photocoagulation, vitrectomy, anti-VEGF (vascular endothelial growth factor) agents, corticosteroids, antiangiogenic therapy, and anti-inflammatory drugs. Surgical therapies, such as intravitreal injections, are invasive and associated with complications such as intraocular bleeding and pain. Usually, intravitreal injections require frequent administration resulting in discomfort, vitreous hemorrhage, and retinal detachment. [18] These expensive and painful treatments, even when they may reduce the risk of vision loss, cannot fully attenuate clinical progression to reverse damage to the retina in the advanced stage of

DR. These shortcomings make it imperative to explore non-invasive routes, novel, and cost-effectiveness for treating DR.

From the current understanding of DR pathogenesis, there are investigations on developing treatments focusing on early diagnostics, natural compound application, and the combination of novel pharmaceutical agents. [11] They focus on the inhibition of neovascularization and the protection of neurovascular degeneration in the retina, gene therapy, and optimization of new ocular drug delivery methods: nanoparticle-based and polymeric drug delivery systems. [12] They provide benefits in optimizing both initiation and maintenance of disease. This review focuses on the importance of developing new non-invasive alternatives for the treatment of DR.

Diabetic retinopathy metabolic abnormalities

In diabetes, hyperglycemia leads to oxidative stress, which plays a critical role in the pathogenesis of DR. The excessive accumulation of reactive oxygen species (ROS) generated by oxidative stress can impair the tissue in and around the retinal vessels. [19] Studies have detected four metabolic abnormalities implicated in DR: 1) activation of the protein kinase C (PKC) pathway, 2) polyol pathway flux, 3) activation of the hexosamine pathway, 4) intracellular formation of advanced glycation and products (AGEs). [20] In addition, they induce mitochondrial aberrations, apoptosis, and inflammatory factors that may elevate hypoxia-mediated VEGF secretion, neurovascular dysfunction, vascular hyperpermeability, and/or neovascularization caused by DR (Figure 1).

Therapeutic agents that show anti-inflammatory and/or antiangiogenic activity have been widely used to alleviate DR-associated complications. [21] In addition, various angiogenic factors such as angiopoietin, erythropoietin, basic fibroblast growth factor (bFGF), insulin-like growth factor (IGF), protein kinase C (PKC), tumor growth factor (TGF), and platelet-derived growth factor (PDGF) have stimulatory or modulating activities during the development of DR. [22]

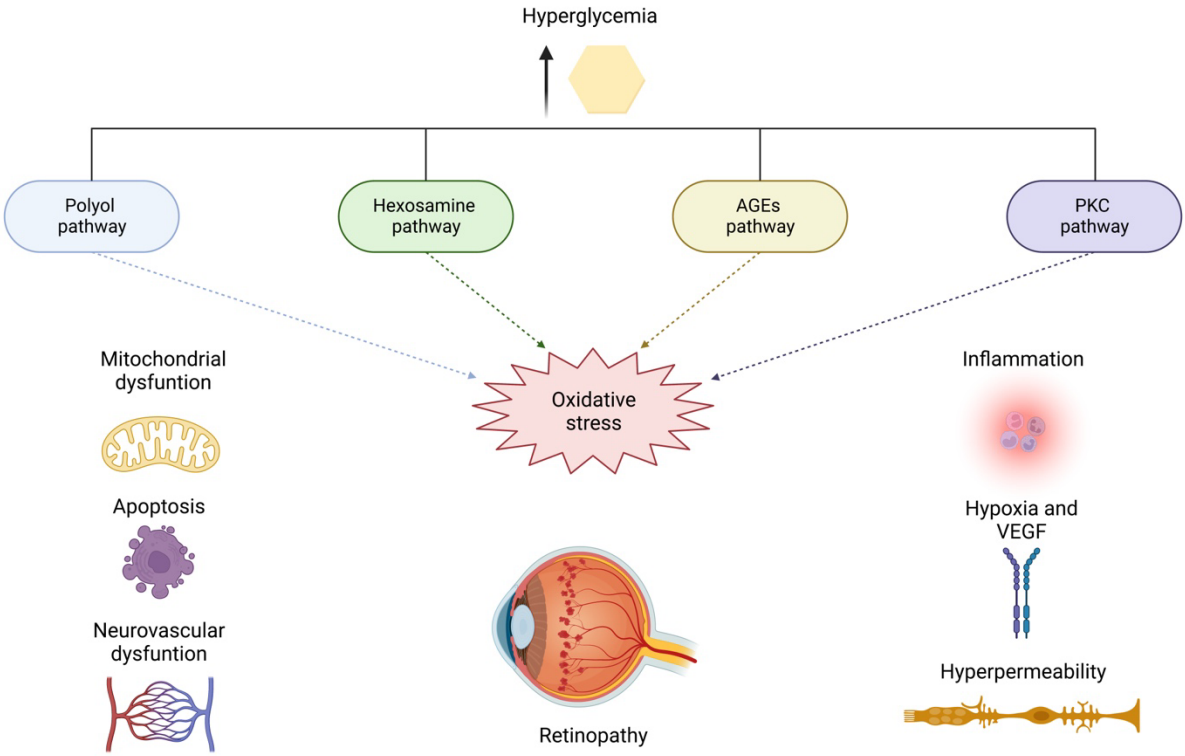

Figure 1 Hyperglycemia associated with poor DR management drives the aberrant regulation of four biochemical pathways in DR patients: the polyol pathway, the hexosamine biosynthesis pathway, the formation of AGEs, and the PKC activation, which contribute to ROS generation and aggravate oxidative stress to promote the pathogenesis of retinopathy. Created with BioRender.com.

Abbreviations: AGEs, advanced glycation end products; PKC, protein kinase C; ROS, reactive oxygen species; VEGF, vascular endothelial growth factor.

Opportunities for diabetic retinopathy treatments

The human eye is vulnerable to different types of damage, whether genetic or acquired. The structure of the eye can be classified into two parts: the anterior segment and the posterior segment.[20] The pupil, cornea, iris, ciliary body, aqueous humor, and lens comprise the anterior segment, whereas vitreous humor, macula, retina, choroid, and optic nerve are parts of the posterior segment. The retina is the nerve layer that receives light, which creates impulses transmitted through the optic nerve to the brain.[23] Ocular

diseases have been treated by two primary modalities: topical drops and intravitreal injections. However, adequately delivering therapeutic agents to the back of the eye (*ie*, the retina) remains challenging.[24]

Currently, new treatment modalities have arisen, and these have served as a source of hope even for patients with advanced DR, where it is calculated that 95% of them could continue with their vision when treated before the retina is severely damaged.[25] They include sustained delivery of therapeutic agents, targeted delivery of drugs to specific cells or tissue, improved delivery of both water-insoluble drugs, large biomolecule drugs, novel pharmaceutical agents, antioxidants, epigenetic, gene therapy, and novel drug delivery systems based on nanoparticles (Figure 2).[26]

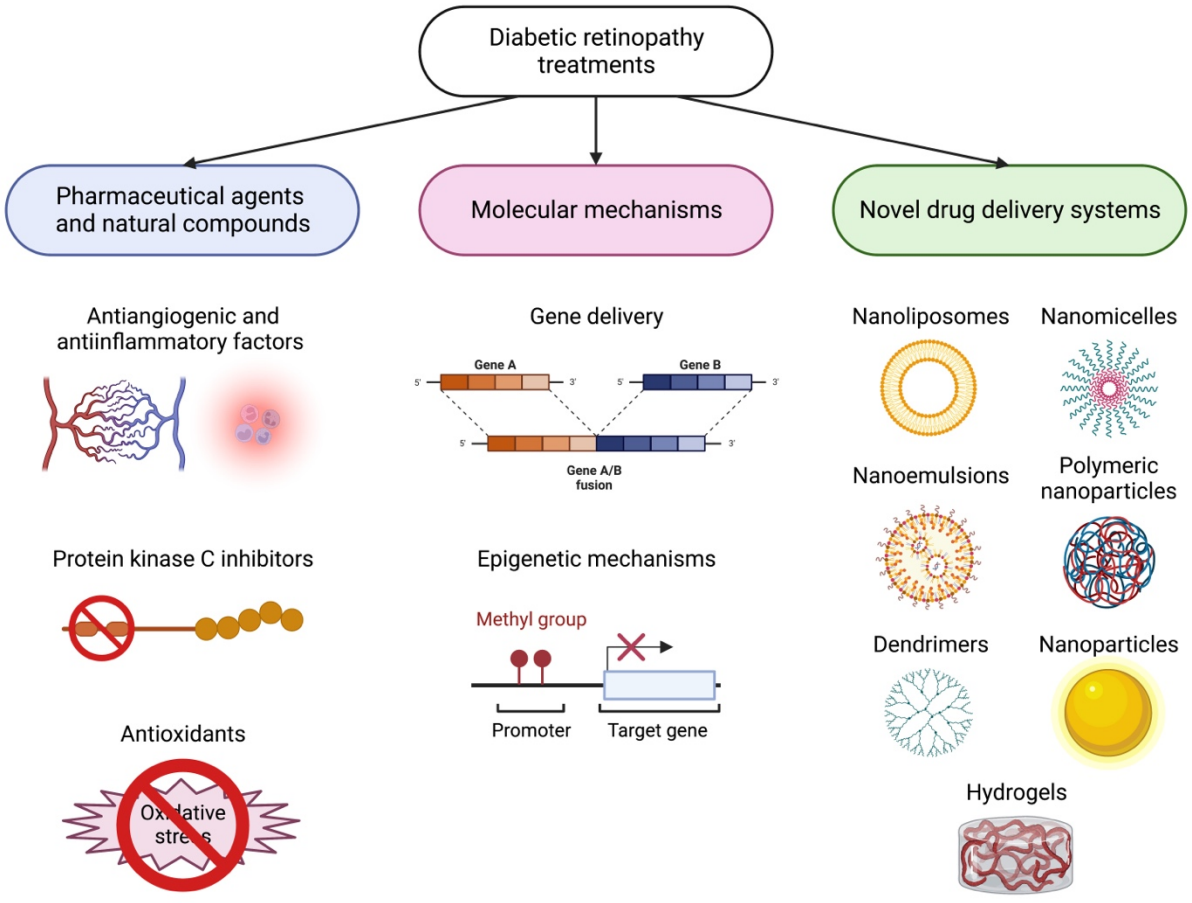

Figure 2 New treatment modalities for diabetic retinopathy exploring pharmaceutical agents and natural compounds, molecular mechanisms, and novel drug delivery systems. Created with BioRender.com.

Pharmaceutical agents and natural compounds for DR treatments

Antiangiogenic and anti-inflammatory factors

Different scientific reports suggest that VEGF is essential in DR development.[27] More specifically, it is possible to find in the literature that this endothelial factor could imply both proliferation and vessel permeability in the progression of PDR. Important levels of VEGF have been found in humans in the vitreous in diabetic patients with PDR. Andreoli and colleagues have shown that the levels of VEGF in the ocular tissues correlate with the number of newly formed vessels.[28] It has also been reported that reducing the VEGF levels makes it possible to prevent the progression of the proliferation stage of the DR.[29] Intravitreal injections of monoclonal antibodies are used to neutralize the VEGF levels for treating ocular diseases, such as PDR, age-related macular degeneration (AMD), and choroidal neovascularization.[30]

Patients with DR significantly increase systemic proinflammatory cytokine expression and an elevation of chemokine synthesis in the retina.[31] For this reason, factors besides VEGF moved into the focus of DR treatment. For example, proinflammatory cytokines and chemokines, like interleukin-1-beta (IL-1β), interleukin-6 (IL-6), and interferon-gamma (INF-γ) released by activated glial cells, were up-regulated in the retina of diabetic animals. Therefore, they seem to be critical for DR development. Interestingly, in DR patients, cytokine and chemokine alterations also seem to play a crucial role. This is reflected in the fact that it was possible to detect an increase of endothelin-1 (ET-1), tumor necrosis factor-alpha (TNF-α), and IL-6 in vitreous samples of proliferative type 2 DM patients via ELISA assay.[32]

Clinical assessment of the use of non-steroidal anti-inflammatory drugs (NSAIDs) has shown a positive effect in attenuating DR symptoms. One is ketorolac, a prostaglandin synthesis inhibitor that targets the cyclooxygenase (COX) family of enzymes. In the clinic, intravitreal and topical administration of ketorolac has been shown to increase visual acuity while reducing inflammatory cytokine production.[33]

Protein C kinase inhibitors

Different studies have shown that the activation of the protein kinase C (PKC) at high levels of diacylglycerol (DAG) because of hyperglycemia is associated with vascular abnormalities in the retina,

kidney, and heart.[34] There are different PKC isoforms, but the β- and δ- isoforms seem to be activated, especially in the vasculature of diabetic animals.[35] It has been reported that in response to hyperglycemia and hypoxia conditions, the VEGF gene transcription is dependent upon PKC activation.[36] Moreover, other pathways involved in developing the DR, such as the release of tumor growth factor-beta (TGF-β) (adhesion molecule) and fibronectin accumulation, are also regulated by PKCs.[37] Some protein C kinase inhibitors have been studied for the management of the DR,[38] for example, ruboxistaurin has revealed promising results in the reduction of visual loss, need for laser treatment, and macula edema progression.[37]

Antioxidants

Many antioxidants have been broadly studied in the literature. These compounds are derived from the diet, such as vitamins C, E, A, and carotenoids.[39] The composition of these antioxidants has presented health benefits related to their consumption. In the last few years, polyphenols have been studied as an important class of antioxidants.[40] Polyphenols, such as phenols, phenolic acids, and flavonoids, are almost present in all plant foods, usually at high levels. Different antioxidants studied to treat DR *in vitro* and *in vivo* are shown below. Recently, substances derived from food have gained attention in medicine.[41]

Curcumin

Curcumin, a yellowish non-flavonoid polyphenol that constitutes the main active compound of *Curcuma longa*, is widely known for its antioxidant and anti-inflammatory properties.[42] Many studies have also described its marked protective effect on retinal cells against oxidative stress and inflammation.[43] Lastly, vitamin D3 levels appear to be lower in type 2 DM patients, which could have therapeutic implications. In diabetic rats and Müller cells, the increase in histone acetylation plays a vital role in regulating the inflammatory response.[44] Therefore, curcumin can exert protective effects on diabetes by inhibiting histone acetylation.[45]

Mauferi A *et al* demonstrated that high glucose induces reactive oxygen species (ROS) production that could trigger oxidative stress, increasing the expression and activity of desoxyribonucleic acid methyltransferase (DNMT). This study also showed that curcumin-based treatment decreased ROS

and DNMT expression levels evaluated in a DR *in vitro* model. These findings suggest that curcumin is a molecule with outstanding potential in DR treatment. [46] Likewise, Yang *et al* administrated curcumin orally for 16 weeks in diabetic-induced rats. These studies showed that curcumin decreases blood glucose levels and the expression levels of VEGF. It also has a protective, antioxidant, and antiapoptotic effect; all of these mechanisms are involved in the development and progression of DR. [47] Huang *et al* studied the protective effect of curcumin on rat retinal vascular endothelial cells (RRVECs) at high glucose concentrations. They evidenced that curcumin reduced ROS and apoptosis markers expression. It also decreased the nuclear factor kappa B (NF-κB) activity and phosphorylated NF-κB activity in the high glucose-induced *in vitro* model. [48]

Resveratrol

Resveratrol (RSV), or 3,5,4'-trihydroxystilbene, is a lipophilic phytoalexin synthesized by plants in response to environmental stress factors such as mechanical injury, harmful ozone exposure, ultraviolet irradiation, and fungal infection. [49] It has excellent properties such as anticoagulant, anticancer, anti-inflammatory, cardioprotective, life-span extending, vessel protective effects, and antioxidant properties. [50] Hence, many studies were carried out regarding the importance of polyphenol in the treatment or prevention of complications related to diabetes. However, the potential therapeutic application of resveratrol remains very limited due to its photosensitivity, poor aqueous solubility (0.03 g/L) at physiological pH, low absorption, rapid first-pass metabolism, and enterohepatic recirculation. [51] Furthermore, it has been demonstrated that, after oral administration of RSV, minimal free compound remains in the plasma and tissues owing to the metabolic breakdown of the compound. [52]

Soo *et al* evaluated the effect of a novel liposome-based drug carrier coencapsulated with RSV-cyclodextrin and compared it to free RSV and a conventional liposomal formulation. After 24 hours, the release profiles were 100% for the new transporter, 40% for free RSV, and 60% for the conventional liposome. The study demonstrates that the co-encapsulation of RSV with cyclodextrin in liposomal formulations is a viable option for the enhanced delivery of hydrophobic chemotherapeutic agents such as RSV. [53] Moreover, Dong *et al* prepared gold nanoparticles (AuNPs) synthesized by green synthesis with RSV as the reducing agent. The prepared nanoparticles were evaluated in diabetic rats. Their findings

demonstrated that the treatment with the AuNPs decreased the permeability of the retina's blood vessels. [54]

Molecular mechanisms for DR treatments

Gene delivery

Gene therapy is designed to introduce genetic material into the cells of patients to compensate for faulty genes or deliver therapeutic transgenes. [55] Over the past three decades, gene therapy has progressed from initial human gene transfer experiments to approved clinical therapies. [56] The goal of gene therapy is to achieve adequate transgene expression at a level to decrease or cure disease conditions with minimal adverse effects. [57] There are several strategies for gene therapy, including gene augmentation, gene-specific targeting, and, most recently, genome editing. [58] Gene therapy has the potential to provide an alternative treatment for DR with distinct advantages, such as a more prolonged therapeutic effect, less injection frequency, the ability to intervene at disease onset, and potentially fewer side effects. [59]

Limited understanding of DR pathogenesis poses a significant obstacle to applying gene therapy at a clinical level. This means gene therapy for DR may need to target a variety of gene candidates implicated in the pathogenesis of DR. Also, DR is a progressive disease with several staging classifications based on the severity of the symptoms over the disease course, which convolutes patient selection criteria. [60] The DR has a multifactorial origin, limiting the management and treatment of this disease. This is the main reason gene delivery has been getting attention because it helps to explore genetic features that affect the oxidation of retinal cells and the activation of the main biochemical pathways. [61] Some of the transgenes used as potential candidates to treat DR are shown in Table 2. [62-66]

Table 2 Summary of potential therapeutic genes introduced into the retina by gene therapy for retinal angiogenesis in rodent models

Transgene	Target	Transduced retinal cell	Animal model	Administration route
Endostatin	Endothelial cell	Müller cell	OIR mouse model	Intravitreal
Angiostatin	Endothelial cell	N/A	OIR mouse model	Intravitreal

PEDF	VEGF	Ganglion, amacrine, horizontal cell	Transgenic mice overexpressing IGF-1	Intravitreal
HIF-1α siRNA, VEGF siRNA	HIF-1α and VEGF	N/A	OIR mouse model	Intravitreal
Amino-terminal fragment, endostatin	uPA/uPAR	N/A	OIR mouse model	Intravitreal

Abbreviations: N/A, not applicable; OIR, oxygen-induced retinopathy; PEDF, pigment epithelium-derived factor; VEGF, vascular endothelial growth factor; IGF-1, insulin-like growth factor-1; HIF-1α, hypoxia-inducible factor-1-alpha; siRNA, small interfering ribonucleic acid; uPA, urokinase-type plasminogen activator; uPAR, urokinase-type plasminogen activator receptor.

Gene therapy may prove a useful adjunct or alternative to conventional treatment for patients with DR. A fundamental problem is the difficulty in designing viable clinical trials and identifying the endpoints that should be used as indicators of therapeutic efficacy. Successful application of gene therapy to DR hinges upon several factors, including a well-defined therapeutic window, safe and efficient vectors, suitable target gene selection, and a reliable means of regulating transgene expression. Rapid developments in all these areas hold promise for beginning clinical trials of gene therapies for DR soon.

Epigenetics modification

Epigenetics refers to gene expression alterations unrelated to deoxyribonucleic acid (DNA) sequence changes, which can be inherited and affected by environmental factors.[67] The epigenetic modification does not change the DNA sequence itself but can regulate gene expression, leading to alterations in phenotype. Previous studies suggested that the four mechanisms of epigenetic modification play significant roles in DR development, including methylation of DNA, histone post-translational modification, non-coding ribonucleic acid-associated gene silencing, and chromatin remodeling.[68]

Ribonucleic acid (RNA) methylation is the earliest discovered mechanism in epigenetic modification. It refers to the addition of methyl groups of S-adenosylmethionine (SAM) to DNA molecules catalyzed by DNMT.[69] Histone modifications refer to methylation, acetylation, phosphorylation, adenylation, ubiquitination, adenosine diphosphate (ADP)-ribosylation, and other modifications of

histones in the presence of related enzymes.[70] Non-coding RNA refers to RNA molecules that do not encode proteins. These RNAs include those with known functions such as ribosomal RNA (rRNA), transfer RNA (tRNA), small nuclear RNA (snRNA), small nucleolar RNA (snoRNA), microRNA (miRNA), and circular RNA, and others with unknown functions such as miRNA, a single strand RNA containing 21-25 nucleotides that are involved in post-transcriptional.[71] Chromatin remodeling refers to epigenetic mechanisms based on altered chromatin conformation.[72] Since the nucleosome is the basic structural unit of chromatin, chromatin remodeling primarily involves structural or molecular changes in nucleosomes, histones, and DNAs during gene expression, replication, and recombination. Chromatin remodeling can affect DNA methylation, replication, recombination, repair, and gene expression.[73]

Novel drug delivery systems

The ocular delivery of drugs presents challenges due to different limitations related to the anatomy and physiology of the human eye. This organ has different barriers preventing exogenous and harmful substances from entering the posterior chamber, particularly the retina and optic nerve.[74] Vision-threatening disorders are mostly related to abnormalities in intraocular tissues, especially in the retina.[75] Nanotechnology presents promising approaches to overcome this situation. This is because nanoparticles have an advantage over classic systems in enhancing the dispensed drug's bioavailability.[76] Nanocarriers, including polymeric micelles, nanoliposomes, nanoemulsions, dendrimers, carbon nanotubes, and hydrogels, could improve therapeutic outcomes in treating DR.[77] These systems and their specific characteristics are presented in this section of the article.

Nanotechnology in retinal drug delivery

Nanotechnology is a technology to study the properties and applications of materials in the range of 0.1 nm to 100 nm.[78] When the material reaches the nanometer size, its properties will change. This material is composed of atoms, molecules, and macroscopic materials. The difference between nanoparticles and bulk materials is mainly due to the relative increase of their surface.[79] Therefore, nanoparticles present several advantages relative to a drug administration alone or classic delivery systems, namely: sustained delivery, targeted delivery to specific cells or tissues, and reduced side effects.[80] In this way,

nanoparticles constitute an innovative and promising therapeutic approach to fulfill the unmet needs for effective and sustained drug delivery to the posterior segment of the eye. [81]

Nanoparticles

Nanoparticles (NPs) can be produced from various materials (*eg*, natural, and synthetic polymers, metal oxides, silica, and noble metals). Polymeric NPs are colloidal particles able to encapsulate (dissolved or dispersed) bioactive or drug molecules, including chemotherapeutic agents, proteins, and nucleic acid, for biomedical applications. [82] Ocular biodistribution of nanoparticles can provide insights into the bioavailability, cellular uptake, duration of drug action, and toxicity. [83] Many factors, such as particle size, composition, surface charge, and mode of administration, influence the biodistribution in the retinal structures and their drainage from the ocular tissues. [84]

Amato *et al* investigated octreotide (OCT), an analog of somatostatin. They linked it to magnetic nanoparticles (MNP-OCT) and tested its effectiveness as a releasing system for treating retinal pathologies such as DR. The results obtained showed that both human retinal endothelial cells (HRECs) and mouse retinal explants (MNPs) can be used as an intraocular delivery system for OCT and that this form of release increases the bioactivity of the active ingredient. [85]

Polymeric nanoparticles

Polymeric nanoparticles are particles within the size range from 1 to 1000 nm composed of a solid polymeric matrix where the drug is either adsorbed on the surface or dispersed in the core of the particles. [86] Polymeric nanoparticles are produced by the polymerization of synthetic monomers or dispersion of natural macromolecules or synthetic polymers. [87] Most commonly used polymers in the formulation of polymeric nanoparticles are poly(lactic-co-glycolic acid) (PLGA), [88] poly(lactic acid) (PLA), [89] chitosan (CS), [90] polyvinyl alcohol (PVA), [91] and poly(methyl methacrylate) (PMMA). [92] These are polymers approved by the Food and Drug Administration (FDA). Out of these, PLGA was popularly used in ophthalmology applications due to its biodegradability, biocompatibility, non-toxicity, and non-immunogenicity. [93] Biodegradable polymer nanoparticles have great potential in ophthalmic drug delivery systems. [94] CS nanoparticles are particularly interested in topically applied polymeric drug delivery systems because CS is a natural polymer, relatively inexpensive, non-toxic, and biodegradable. [95] CS has strong mucoadhesive properties because of its ionic interaction between the positively charged amino

groups of chitosan and the negatively charged sialic acid residues of mucin. CS nanoparticles show a longer retention time and greater penetrability in the ocular membrane. [95]

Sandri *et al* investigated chitosan solid lipid nanoparticles (CS-SLNs) to improve the residence time of colloidal systems in the precorneal area through mucoadhesive interaction. These findings demonstrate that CS-SLNs have enhanced mucoadhesion, leading the way for a high-performing ophthalmic formulation. [96] In addition, Lopez *et al* developed PLGA nanospheres conjugated with polyethylene glycol (PEG) in a process called PEGylation. These nanospheres were loaded with dexibuprofen to be used as an anti-inflammatory drug for ocular administration. The results obtained showed an *ex vivo* corneal and scleral permeation profile, highlighting significant retention and permeation of the drug in the corneal tissue than in the sclera. They demonstrated that these nanospheres could be promising for their use in treating ocular inflammatory diseases. [97] Finally, a design and optimization of melatonin-loaded lipid-polymer hybrid nanoparticles (mel-LPHNs) were proposed by Romeo *et al*, and this system consisted of PLGA-PEG polymer nanoparticles coated with a cationic lipid shell. This design ensures an effective drug delivery, antioxidant effect on HRECs and capability to improve the efficacy of melatonin in preventing the glycemic insult on HRECs. [98]

Nanoliposomes

Nanoliposomes are small artificial vesicles with a spherical shape consisting of single or multiple lipid bilayers formed from natural or synthetic phospholipids with an aqueous core. [99] They are used as vehicles for the administration of both lipophilic (bilayer loaded) as well as hydrophilic (core-loaded) drugs. [100] Liposome properties markedly depend on lipid composition, fluidity of the bilayers, size, surface charge, and preparation method. Nevertheless, their application is limited due to the short shelf life, limited drug loading, and difficulty in sterilization. [101]

Bevacizumab (Avastin®), an anti-vascular endothelial growth factor, was developed by Malakouti-Nejad *et al*, and is one of the most potent medications used to suppress ocular angiogenesis. Nanoliposomes were used to increase the availability of bevacizumab (BVZ) during therapy. The BVZ-containing optimized formulation (NLPBVZ) was described, and its safety was determined. The permeability of the nanoliposome was examined using emerging retinal pigment epithelial (ARPE) cells. The NLP-structural BVZ's stability and integrity were also calculated. The formulation did not negatively

impact human umbilical vein endothelial cells (HUVECs) and ARPEs. Further evidence that the structural integrity of the protein was preserved after encapsulation came from the circular dichroism (CD) pattern and intrinsic fluorescence spectra. According to the research, the molecule was rendered safer, more stable, and hence suitable for treating eye problems by being entrapped into nanoliposomes. [102]

Kaiser *et al*, on the other hand, developed a nanoscale variation of an anionic, cholesterol-fusing liposome that can contain therapeutic quantities of minocycline and be used for drug administration. They proved that size extrusion, followed by size-exclusion chromatography, could form a sustainable 80-nm liposome that contained minocycline at a concentration of 450 ± 30 μM, which is 2–3% of the loading material. More crucially, in the STZ model of Diabetes, these non-toxic nanoliposomes may transfer 40% of the encapsulated minocycline to the retina, followed by subconjunctival injection. The effectiveness of therapeutic medication delivery was evaluated using transcriptome and proteomic biomarker panels. Proinflammatory diabetic indicators were downregulated in response to both free and encapsulated minocycline treatments at both the messenger RNA and protein levels, demonstrating the value of biomarker panels for evaluating ocular medication delivery systems. [103]

Nanoemulsions

Nanoemulsions are defined as oil-in-water type emulsions, in which tiny droplets form with lipid core inside and outer lipid membrane. [104] These structures are stabilized using surfactants, which, along with the small size of nanoemulsions, provide increased membrane permeability, thus higher penetration in the deeper layers of the ocular structure and facilitated drug uptake. Surface-modified nanoemulsions using suitable polymer can also provide a sustained release effect. [105] This system has the advantage of having better therapeutic action, fewer side effects, and more patient compliance. Nevertheless, nanoemulsions are unsuitable for long-term sustained drug release. [106]

Hussein *et al* developed an oil-in-water nanoemulsion based on carvacrol with Tween 80 as a nonionic surfactant. The obtained nanoemulsion presented a very small diameter with high monodispersity. The *in vivo* study indicated an improvement in fasting blood sugar, same as a reduction in insulin in diabetic-induced rats concomitant with alterations in oxidative stress parameters and elevation of homocysteine (Hcy) level. Carvacrol-based nanoemulsion is considered a promising agent that offers a treatment to attenuate hyperglycemia and neurodegenerative diseases. [107]

To assess the effectiveness of antisense oligonucleotide (ODN17) cationic nanoemulsion aimed at VEGF-receptor-2 (VEGF-R2) in reducing neovascularization, Hagigit *et al* used mouse and rat models for retinopathy of prematurity (ROP) and corneal neovascularization. Rat eyes exposed to a saline solution or scrambled ODN17 solution exhibited the highest level of corneal neovascularization. While there was no significant difference between the groups treated with saline and the scrambled ODN17 control solution groups in the groups treated with blank nanoemulsion or scrambled ODN17 nanoemulsion, the groups treated with ODN17 solution or Avastin® (positive ODN17 control) elicited a marked significant inhibition in corneal neovascularization, confirming the results reported in the literature. In addition, the eyes treated with the ODN17 nanoemulsion group showed considerably stronger prevention of vitreal neovascularization (64%). Overall, the findings suggest that cationic nanoemulsion may be viewed as a promising prospective ocular delivery method and an effective therapeutic tool of significant clinical value in the prevention and upcoming treatment of ocular neovascular disorders. [108]

Nanomicelles

It consists of amphiphilic molecules that self-assemble in aqueous media to form organized structures where the polar head groups are in contact with the surrounding solvent, and the hydrophobic single-tail regions are oriented toward the nanomicelle center. [109] The self-assembly occurs at concentrations higher than the critical micelle concentration (CMC). Nanomicelles are similar to liposomes: whereas liposomes are composed of lipid bilayers, nanomicelles are made of monolayers. [109,110] In ocular drug delivery, nanomicelles offer unique advantages due to their nanoscale size and increased permeation through ocular epithelia with reduced or no-reduced irritation. Nanomicelles can be formed with either surfactant (anionic, cationic, nonionic) or polymeric systems. [111] Polymeric micelles that can deliver the drug to specific sites in the human eye have recently gotten scientific attention. [112] These promising nanosystems can provide advantages related to high permeation and longer residence time as they have significant drug absorption through ocular barriers. [113] Some publications mentioned that mucoadhesive properties of micelles formed from biopolymers enhance the bioavailability of the drug since they improve the contact time with the eye structures and minimize their elimination. These physicochemical properties are also fundamental in topics related to industrial production and patient compliance. [114]

Moreover, the fabrication techniques for polymeric micelles are simple and cost-effective, improving physical stability that satisfies the requirements for industrial acceptance. One of the crucial developments in these formulations allows for their application as eye drops without affecting the vision and discomfort of diabetic retinopathy patients. [115] For diseases that affect the posterior eye segment, such as DR, the micelles should reach it by trans-scleral route around the conjunctiva until they contact the retina.

Alvarez-Rivera *et al* studied a micelle-based formulation to improve the solubility, stability, and corneal permeability of α-lipoic acid (ALA). The formulation of nanomicelles prepared showed improvements in the permeability of the cornea where the accumulation of ALA was evidenced, as well as a drug flow increment in the receptor chamber. Therefore, this study demonstrates that the formulation based on nanomicelles improved the release of ALA, which shows the potential of this type of formulation in the research of new non-invasive intraocular delivery systems. [116]

Rassu *et al* develop amphiphilic inulin-D-tocopherol succinate bioconjugates (INVITE) and curcumin-loaded nanomicelles known as INVITE C. They were tested to see if they could offer a treatment for the bilateral damage to retinal blood vessels that diabetic retinopathy causes. INVITE C is degraded by enzymes, yielding -tocopherol, which has antioxidant potential, according to *in vitro* sensitivity to enzymatic hydrolysis and antioxidant activity. INVITE C also has strong antioxidant action. Furthermore, transport studies on polarized monolayers of human retinal pigment epithelium (HRPE) cells provide evidence of active efflux of curcumin, in free or encapsulated forms, from apical to basolateral sides. Last but not least, INVITE C appears to maintain the HRPE monolayer's transepithelial electrical resistance, whose values were significantly reduced by high glucose circumstances. [117]

Chitosan oligosaccharide-valylvaline-stearic acid (CSO-VV-SA) nanomicelles were developed by Xiaoyue Xu *et al* They were created based on the active targeting of the peptide transporter-1 (PepT-1) for topical ocular medication delivery. Hydrogenated castor oil-40/octoxynol- 40 (HCO-40/OC-40) mixed nanomicelles were also developed. Human conjunctival epithelial cells (HCEpiC) and corneal epithelial cells (HCEpiC) were not significantly affected by either nanomicelle's cytotoxicity (HConEpiC). Frozen section *ex vivo* fluorescence pictures showed that the nanomicelles mostly reached the posterior segment through the conjunctival pathway. Dexamethasone (DEX) from both nanomicelles may be identified for

more than 3 hours in rabbit tears, according to an *in vivo* precorneal retention investigation. The delivery effectiveness of CSO-VV-SA nanomicelles was not less effective than that of HCO-40/OC-40 mixed nanomicelles, according to an *in vivo* distribution evaluation of rabbit eyes. [118]

Dendrimers

Dendrimers are organic branched tree-like structures. Dendrimer morphology is characterized by compromising a core that is the starting site of the branching. [119] Dendrimers can be classified depending on the branching cycles defined when they are synthesized on a nanometer scale approximately 2-10 nm in diameter. [120] Dendrimers have several advantages: they encapsulate a poor water-soluble drug into the internal cavities, dendrimer size, and low polydispersity index, uptake by the reticuloendothelial system (RES) can be avoided, improve solubility, permeability, and retention effect, anionic and neutral surface dendrimers are in lack of cytotoxicity and ocular irritation and targeting efficiency. [121] At the end of each, there are surface functional groups, which can be the binding locations for drug molecules, imaging agents, or targeting molecules.

The compounds usually used for dendrimer synthesis are polyamidoamine (PAMAM) and polypropylene imine (PPI). In the design of drug delivery systems, the PAMAM dendrimers are suggested since amine functional groups can be easily bound to a drug. [122] This could occur in different modalities, such as ionic interactions, direct conjugation, or trapping in the core of the particle. The building blocks used determined the dendrimer morphology and size. [123] This characteristic makes dendrimers so versatile that they can be designed to carry an extensive range of therapeutics to an extensive range of targets. Specifically, this versatility has been focused on developing dendrimers for numerous routes of administration for ocular drug delivery. [124]

In fact, Kambhampati *et al* explored a PAMAM-triamcinolone acetonide (TA) dendrimer conjugate, which is an antiangiogenic and anti-inflammatory agent. This research aimed to improve its intravitreal administration for treating DME, PDR, and exudative macular degeneration. The results showed that dendrimer-based administration could improve the efficacy of TA, having positive effects on the reduction of inflammation and VEGF production. [125] Likewise, Yavuz *et al* studied the effects of PAMAM dendrimers on the ocular absorption of DEX. The ocular pharmacokinetic properties of DEX formulations were studied in an *in vivo* model after topical and subconjunctival applications to evaluate

the effect of PAMAM on DEX delivery in rat retinas. The results showed that the formation of complexes with PAMAM dendrimers improves the transport and bioactivity of DEX through the tissues of the cornea and sclera. These findings indicate that dendrimers are an alternative with great potential for developing new intraocular drug delivery systems. [126] The same authors evaluated a sustained-release DEX conjugate formulation with enhanced ocular permeation using PAMAM dendrimers (DEX-PAMAM). They evaluated the drug release of the formulations and their cytotoxicity in ARPE19 cell lines. Their findings showed that DEX-PAMAM dendrimers improved ocular permeability and DEX levels in ocular tissue after subconjunctival injection. [58]

Cho *et al* studied generation-4 hydroxyl polyamidoamine dendrimer nanoparticles to deliver TA for microglia activation in the ischemic retina in a mouse model of oxygen-induced retinopathy (OIR). After intravitreal injection of the system, sustained retention in activated microglia is observed in disease-associated retinal areas and a decreased production of inflammatory cytokines, microglial activation, and preretinal neovascularization in the OIR model. The results of this research showed that targeted therapy based on dendrimers, and specifically dendrimer-conjugated TA, constitutes a promising treatment approach for DR, offering increased and sustained pharmacological efficacy. [127]

Hydrogels

Hydrogel is a three-dimensional (3D) network made of polymeric materials that provides a highly moist environment. [128] This biomaterial has been exploited to encapsulate, deliver, and preserve therapeutic compounds, including cells. Therefore, it is necessary to develop innovative delivery methods to enhance the field of ophthalmology. [129] Apart from ocular delivery systems such as dendrimers and polymeric micelles, hydrogels are another type of vehicle that bring favorable properties for drug release. [130] The most important properties of these materials are related to their three-dimensional network that contains polymer chains and their high capacity for water retention. It is possible to design different types of hydrogels altering properties such as stimuli-responsiveness to heat, light, and pH. These changes benefit drug loading with controllable release mechanisms in ophthalmology. [131] Different types of hydrogels have been tested in DR.

Alvarez-Rivera *et al* designed hydrogels as contact lenses for the local treatment of ocular pathologies related to diabetes, adding bioinspired aminopropyl functional groups. Epalrestast, an aldose

reductase inhibitor, was used to interact with these functional groups. Bovine cornea permeability tests demonstrated that epalrestat released from hydrogels could efficiently accumulate in the cornea. The results obtained also demonstrated anticataract activity in *in vivo* and *in vitro* diabetic eye models. These findings evidence that hydrogels are a potential alternative for developing new non-invasive intraocular drug delivery systems. [132]

Imai *et al* synthesized N-isopropyl acrylamide units with dextran macromer and oligolactate-(2-hydroxyethyl methacrylate) units by ultraviolet (UV) photopolymerization. The hydrogels were loaded with insulin during synthesis, and their release was tested in diabetic rat retinas. The results of this study showed that these hydrogels could maintain the release of insulin in the retina through subconjunctival implantation, and it has a direct effect on the prevention of the development of diabetic retinopathy caused by hyperglycemia. [133] Turturro *et al* investigated the effect of injections of a PEG diacrylate (PEG-DA) crosslinked poly N-isopropylacrylamide (PNIPAAm) hydrogel on retinal function in an *in vivo* model and evaluated retinal function after hydrogel injection. The result of this research suggests that this hydrogel injection produces a small transient effect on retinal function without any long-term effect. These results show the potential of PNIPAAm-based materials as an ocular drug delivery platform. [134]
Hydrogel could be a potential contact lens implant for retinal drug delivery for DR, and this idea was developed by the Sadasivam research group. They demonstrate that poly (2-hydroxyethyl methacrylate) (pHEMA) and CS hydrogels are effective carriers for ocular drug delivery for retinopathy as non-invasive implants. [135]

Conclusion

Diabetic retinopathy is a human eye disease that causes changes in retinal blood vessels, leading to bleeding, leak fluid, and vision impairment. Retinopathy symptoms include blurred vision, color perception changes, red spots, and eye pain. DR can become a serious threat representing a significant change in quality of life of diabetic people, socioeconomic cost for healthcare systems in the present and a challenge for the future. Considering the anatomy and physiology of barriers in the eye and treating and managing pathologic ocular neovascularization in the posterior segment of the eye in DR is a challenging task. Therapy minimally invasive with prolonged efficacy remains a major unmet medical need for patients

with DR. However, and the novel pharmaceutical agents focus on the inhibition of neovascularization, oxidative stress, and protection of neurovascular degeneration in the retina. Antioxidants, epigenetic mechanisms, gene therapy, and optimization of new ocular drug nanotechnology-based delivery systems have possibilities for wide application in retinopathy because they can pass through barriers in the eye. We need these novelty and unconventional therapies for DR, but further research and evaluation before human trials begin will need to be done.

Acknowledgments

The authors thanks to the EIA University and the Ministry of Science, Technology, and Innovation of Colombia support under project registration code: 133384468146 and announcement 402-2020.

Disclosure

The authors report no conflicts of interest in this work.

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