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Mini-review

Unraveling diabetic retinopathy: mechanisms, novel targets, and the need for continued innovation

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Diabetes is a chronic disease and it is a group of metabolic disorders characterized by elevated levels of blood glucose, which results in microvascular complications. The most frequent consequence of microvascular complications is diabetic retinopathy. The pathophysiology of diabetic retinopathy is multifactorial and is associated with several interdependent mechanisms, involving the interplay between hyperglycemia, hyperlipidemia, hypoxia, reactive oxygen species (ROS), inflammation, and neovascularization. Diabetic retinopathy is largely asymptomatic and, by the time-impaired vision is experienced, the pathology may be significantly advanced from non-proliferative to more severely proliferative, in which the abnormal growth of new vessels occurs. Treatment options for diabetic retinopathy include laser treatment, vitrectomy, and a single or a combination of medications. Artificial intelligence tools and Gene editing are futuristic ways of approaching retinopathy treatment. These treatments and techniques either need the use of anesthesia or long-term hospitalization, or to be injected repeatedly and can cause mild discomfort and systemic side effects. The anti-vascular endothelial growth factor alone or with steroids showed some therapeutic benefits. The treatment for diabetic retinopathy is still challenging. Continuous research and development in this field are crucial to improve outcomes for individuals affected by retinopathy, reducing the burden of this vision-threatening complication of diabetes.

Keywords: Microvascular complications, Artificial Intelligence, Blindness, Polyols, Sorbitol

Introduction

Diabetes is a chronic (lifelong) disease and is a group of metabolic disorders characterized by an elevated level of blood glucose. Globally, there are approximately 537 million adults living with diabetes. By 2030 and 2045, this number is anticipated to reach 643 million and 783 million, respectively[1]. Diabetes complications that could be fatal can arise from consistent hyperglycemia conditions. Diabetes is closely linked with both microvascular and macrovascular complications. Microvascular-related retinopathy, neuropathy, cardiovascular, cerebrovascular, and peripheral vascular diseases related to macrovascular disease cause damage to organs and tissues in patients[2]. The most prevalent microvascular complication of diabetes is retinopathy (DR) most likely cause of vision impairment[3]. The metabolic anomalies brought on by hyperglycemia, enhance the formation of (AGEs), and the generation of ROS and promote retinopathy[4] (Fig. 1). In 2020, the number of adults globally with DR, vision-threatening DR, and macular edema was estimated to be 103.12 million, 28.54 million, and 18.83 million, respectively by 2045, the numbers are expected to rise to 160.50 million, 44.82 million, and 28.61 million, respectively[5]. A key factor in diabetes patients acquired blindness it has been established that one important factor of DR is oxidative stress. The metabolic disorder brought on by hyperglycemia alters different pathways leading to DR[4,6].

Methodology

A literature search was conducted to identify preclinical, clinical, and regulatory evidence related to diabetic retinopathy, its pathophysiology, and current/emerging treatment modalities. Searches were performed in PubMed, Scopus, Web of Science, Google Scholar, and ClinicalTrials.gov up to May 2025. Inclusion criteria for the literature review include articles published in English. Articles that give information about preclinical and clinical studies

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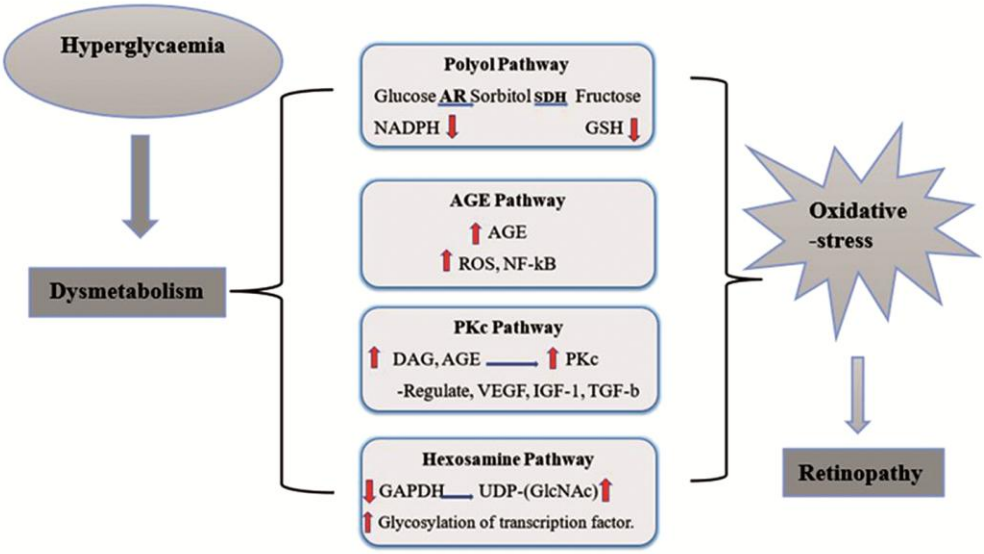

Fig. 1 — The metabolic anomalies brought on by hyperglycemia enhance the formation of (AGEs), and the generation of ROS, and promote retinopathy.

(Phase I–IV), including systematic reviews, meta-analyses, RCTs, and major guideline documents. Studies evaluating pharmacological agents, laser approaches, anti-angiogenic therapy, monoclonal antibodies, AI tools, and gene-based interventions. This manuscript does not include non-peer-reviewed articles except regulatory documents, Case reports, and small case series unless directly relevant and non-ophthalmic diabetes complications.

Classification Of Diabetic Retinopathy

DR is largely asymptomatic and, by the time impaired vision is experienced, the pathology may be significantly advanced. There are two types of DR, proliferative DR (PDR) and non-proliferative DR (NPDR)[7]. Clinical signs of vascular anomalies in the retina help in the diagnosis of DR, based on the degree of micro-vascular degradation and associated ischemia damage[8]. Only in severe stages of diabetic macular oedema (DME) and/or PDR does vision loss occur. The severity of DR ranges from non-proliferative and pre-proliferative to more severe PDR[9]. Neovascularization develops during the PDR stage[10]. This begins on the venous side of the retinal circulation and may cross the inner limiting membrane into the vitreous. If left untreated, these new blood vessels can be surrounded by fibrous connective tissue and become brittle and leaky. This fibrous tissue and the posterior hyaloid often adhere, which might result in vitreous hemorrhage[11]. DME

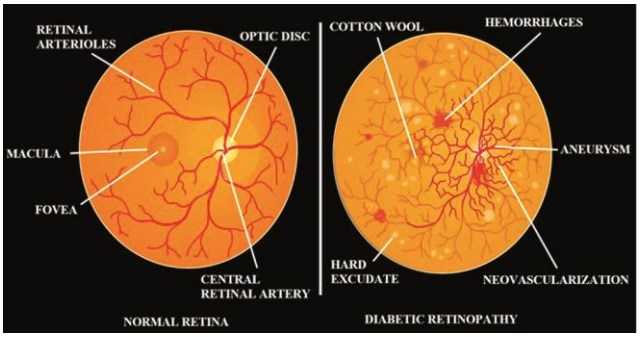

Fig. 2 — Pathological lesions of diabetic retinopathy. A schematic illustration of the normal retina compared with DR (NPDR/PDR) with DME.

arises when the blood-retinal barrier (BRB) breaks compromised because of diabetes, allowing fluid and circulating proteins to flow into the neuronal retina[12,13] (Fig. 2).

Pathophysiology

Chronic hyperglycemia, which results in capillary damage, increased vascular permeability, vascular leakage, and edema, is the cause of the microvascular complications of diabetes[14]. Several interdependent mechanisms and pathways associated with hyperglycemia promote the pathogenesis of DR, including the polyol pathway, the Hexosamine pathway, and activation of protein kinase (PKC)[15]. Additionally, extracellular matrix (ECM) formation takes place, thickening the basement membrane,

pericyte loss, and the development of microaneurysms[16], raising the risk of blockage and ischemia. Compensatory growth of abnormal new blood vessels that are fragile and prone to hemorrhage also occurs[17].

Polyol or sorbitol pathway

Under hyperglycemia, the polyol pathway of glucose metabolism is initiated. The first enzyme in this route, aldose reductase, uses NADPH as an electron donor to transform glucose into sorbitol, which is subsequently oxidized to fructose by sorbitol dehydrogenase with the help of NAD+, transformed to NADH[18]. First, the hydrophilic alcohol sorbitol is powerful and cannot permeate into lipid membranes, causing cell hypertonicity and an increase in osmotic pressure, which causes osmotic damage and cell death in retinal capillaries. Second, the fructose produced by the polyol pathway can be transferred into fructose-3-phosphate through phosphorylation and then broken down into 3-deoxyglucosone. Both products can then be used as precursors to help with the glycosylation process that results in the accumulation of advanced glycation end products (AGE)[19]. Excessive NADPH usage reduces the cofactors needed to produce glutathione (GSH), weakening the body's ability to fend off oxidative stress. When sorbitol dehydrogenase consumes NAD+ in excess, the ratio of NADH to NAD+ shifts abnormally. Excess NADH can then be used as a substrate by NADH oxidase, which helps retinal cells produce intracellular ROS[20]. However, ponalrestat and sorbinil ARIs are not effective in preventing the development of retinopathy in human clinical trials[21,22] (Fig. 3).

Nonenzymatic Protein Glycation

Normally, AGEs begin to grow at a gradual, steady rate throughout embryonic development and continue to build up over time. However, because there is more glucose available in diabetes, its formation is significantly accelerated[23]. The nonenzymatic interaction between reducing sugars and free amino groups of proteins, lipids, and nucleic acids results in the heterogeneous group of compounds known as AGEs[24]. A Schiff base, the first by-product of this reaction, spontaneously rearranges into an Amadori product[25]. A crucial property of certain processes or precursor AGEs is their capacity to produce covalent crosslinks between proteins, which change the structure and function of proteins, as in cellular matrix, basement membranes, and vessel-wall components[26]. The formation of AGEs is facilitated by the glycosylating substances fructose-3-phosphate and 3-deoxyglucosone by-products of the polyol pathway. The interaction of AGEs with several cell-surface AGE-binding receptors, such as the receptor for advanced glycation end products (RAGEs), results in cellular activation and pro-oxidant, pro-inflammatory responses[27].

Hexosamine Biosynthesis Pathway (HBP)

Recent research indicates that insulin resistance and DR may be partially caused by the metabolism of glucose through the HBP[28]. When there is too much intracellular glucose that cannot be removed by glycolysis, the hexosamine pathway is activated. Most glucose is converted to glucose-6-phosphate when it is present in high concentrations within the cell, and this compound is then changed into fructose-6-phosphate[29]. When blood sugar levels are

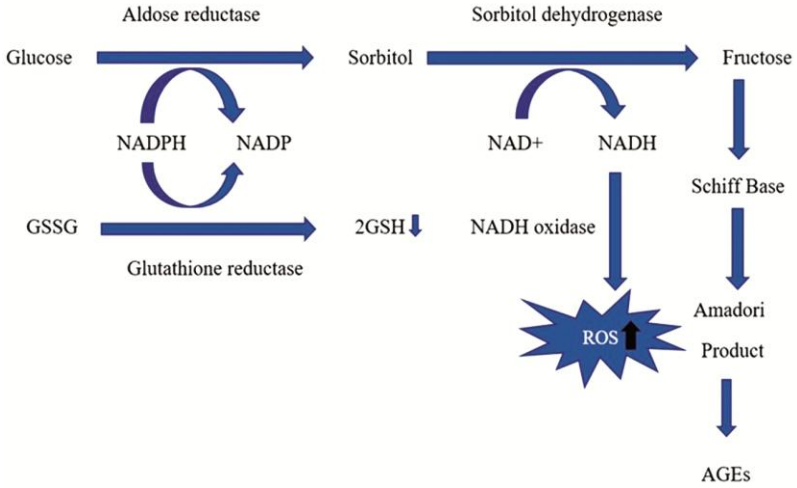

Fig. 3 — Polyol pathway formation of AGE contributes to ROS generation.

high, the enzyme glutamine fructose-6-phosphate aminotransferase (GFAT) converts fructose-6-phosphate to N-acetyl glucosamine-6-phosphate, but when blood sugar levels are low, a tiny portion of glucose is metabolized by the hexosamine route. Glucosamine is more potent than glucose in stimulating TGF-b[30]. The rapid metabolism of glucosamine-6-phosphate that results from the flux of glucose in this pathway results in the formation of uridine diphosphate N-acetylglucosamine (UDP-GlcNAc), which appears to be the cause of changes in protein function and gene expression[31] that can lower cell protection and ultimately cause cell apoptosis in retinal neurons and endothelial cells, (Fig. 4).

Protein Kinase C

Diacylglycerol (DAG) and PKC are essential intracellular signal transduction molecules that can control a variety of vascular processes, including permeability, the release of vasodilators, endothelial activation, and growth factor signaling. Phospholipase C is activated, which raises the levels of Ca+2 and DAG, which then trigger receptor-mediated physiological activation of PKC[32]. Diabetes may lead to pathological PKC activation. In the diabetic condition, increased glucose levels will speed up the glycolytic pathway flow and raise the levels of intracellular glyceraldehyde-3-phosphate. An increase in this intermediate's concentration can promote an increase in the de novo synthesis of DAG via glycerol-3-phosphate[33]. These persistently high levels of DAG can then activate PKC; additionally, AGE and ROS may indirectly activate PKC. DAG-PKC activation levels are elevated in a variety of tissues in diabetic animals[34]. More specifically, the root cause of diabetes has been associated with two PKC isozymes, PKC δ and PKCβ. Whereas PKC δ affects insulin resistance and beta-islet cell activity, which leads to diabetes, and PKCβ is a major factor in diabetic microvascular complications[35,36]. Variations in blood flow and PKC activation may both contribute to the stimulation of growth factor expression (VEGF, TGF-**β**). Furthermore, MAP kinase-dependent signaling pathways can be affected by PKC activation[37,38]. Both the retina of diabetic rats and cultured vascular cells exposed to high glucose levels exhibited PKC activation. The increased synthesis of DAG in retinal micro-vessels brought on by elevated blood glucose levels may be the mechanism underlying PKC activation[33]. Cytokine activation and inhibition, vascular changes, and aberrant angiogenesis linked to diabetes microvascular complications are all caused by faulty PKC signalling, **(**Fig. 5).

Receptor for advanced glycation products (RAGEs)

AGEs refer to a class of substances created by a series of processes, the first of which is the nonenzymatic interaction between the free amino group of proteins, lipids, or DNA and the carbonyl group of reducing sugars[39].The activation of the NFκB and MAP kinase pathways by AGEs results in a rise in the expression of pro-inflammatory cytokines like TNF-α and IL-1β[40,41]. Diabetes accelerates the accumulation of AGEs, which is connected to DR[42]. Benfotiamine has an impact on the HBP pathway in addition to inhibiting the production of AGE, which assists in preventing the development of DR[43]. In animal models, benfotiamine has been demonstrated to enhance ECM turnover, prevent human pericyte apoptosis, and reduce retinal capillary changes, underscoring the drug's potentially beneficial effects in DR[44,45].

Inflammation

An important part of the etiology of DR is inflammation. Multiple cases of chronic low-grade

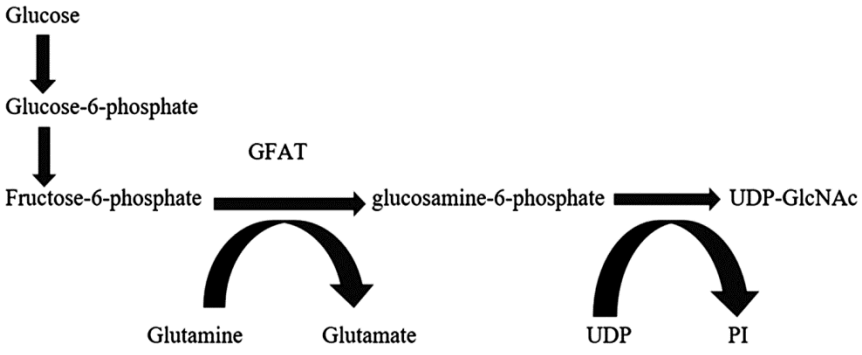

Fig. 4 — Hexosamine pathway formation of UDP-GlcNAc, which alters gene expression in retinal neurons and endothelial cells.

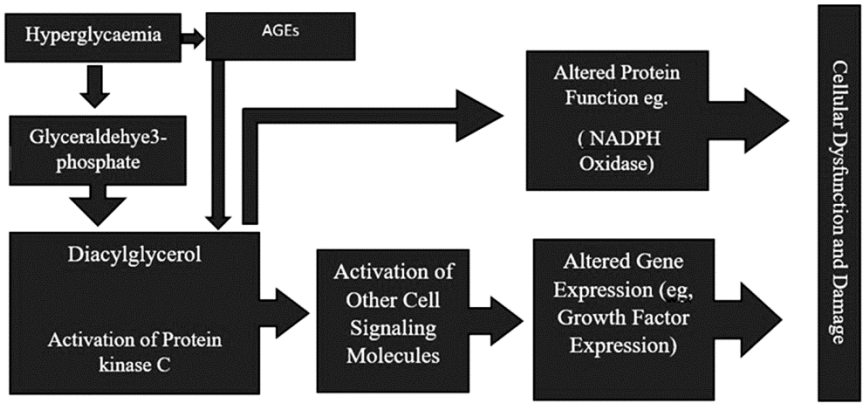

Fig. 5 — Protein Kinase C signalling pathway.

inflammation have been found in people and diabetic animal models at various stages of DR[46]. DME mechanism initiates with advanced glycation end products to modify the ECM and increase vascular stiffness. Additionally, and more importantly, they activate the endothelial membrane receptors for advanced glycation end-products (RAGE), triggering several metabolic pathways (signaling pathways) that ultimately increase the expression of molecules like inflammatory intercellular adhesion molecule-1 (ICAM1) and VEGF as well as a synergistic reduction in nitric oxide (NO), resulting in oxidative stress in pericytes and causing their apoptosis, capillary vasoconstriction, elevated leukocyte adhesion leading to hypoxia, and retinal capillary hyperpermeability[47].

Treatments

The gold standard for treating DR is laser treatment, the first intraocular procedure to offer a highly successful technique for minimizing vision loss in diabetic patients[48]. PDR laser therapy typically does not result in improved vision; it is intended to prevent further vision loss. The laser directly treats leaking blood vessels by securing the leakage site (photocoagulation) or by removing aberrant newly created blood vessels that have grown in the retina's periphery but are not necessary for functional vision. Vascular endothelial growth factor (VEGF) is responsible for the creation of aberrant blood vessels. Recent animal studies on mice with chemically ablated photoreceptors showed reduced hypoxia and increased retina function, which provided additional support for this concept[49,50]. Although intrusive laser photocoagulation has been found to slow the progression of vision loss, it hardly improves or restores vision. Thus, treatment with anti-angiogenic agents was applied to improve vision loss in patients with PDR as well as DME[51]. Intraocular treatment modalities for diabetic eye disease include laser photocoagulation, intra-vitreous injections of anti-VEGF and steroid agents, and vitreoretinal surgery, currently available treatment of advanced disease, once PDR or DME has developed[52].

Anti-angiogenesis therapy

Vascular endothelial growth factor Inhibitor (VEGF inhibitor)

VEGF inhibitors have revolutionized the way DR is treated. Presently, anti-VEGF drugs authorized by the U.S. FDA, ranibizumab, aflibercept, and unapproved intravitreal bevacizumab have all been studied in clinical studies for the treatment of DR. Ranibizumab has undergone the most comprehensive assessment in clinical trials among all these drugs. According to the findings of the RESOLVE and RESTORE studies, intravitreal ranibizumab produced better improvements in Best-corrected visual acuity (BCVA) in clinically severe DME conditions than laser monotherapy[53,54]. In the VISTA and VIVID trials, intravitreal aflibercept provided greater visual results for DME patients than standard laser therapy[55]. However, anti-VEGF therapy's drawbacks and side effects are also a major source of worry. Anti-VEGF medicines have a limited half-life; thus, monthly, or biweekly injections are required to maintain potency. Frequent injections may raise the risk of endophthalmitis, an uncommon side effect of intravitreal injection[56] (Table 1).

Other anti-angiogenesis therapy

Along with VEGF inhibitors, many anti-angiogenic drugs are currently being studied in clinical trials. Squalamine improved vision recovery in macular

Table 1 — VEGF-Inhibitor and Non-specific anti-angiogenic drug

Class	Drug	Status	Adverse Effects
VEGF-Inhibitors	Ranibizumab	FDA approved	a) Ocular hypertension b) Preretinal hemorrhage c) Edema
	Pegaptanib (Sultan et al., 2011)	FDA approved	a) Conjunctival hemorrhage b) Ocular hypertension
	Aflibercept (Heier et al., 2016b)	FDA approved	a) Ocular hypertension b) Preretinal hemorrhage c) Edema
	Bevacizumab (Wells et al., 2016)	Off-label use	a) Ocular hypertension b) Preretinal hemorrhrage c) Edema
Non-specific anti-angiogenic	AKB-9778 (Tie2 activator) ID: NCT01702441	Completed	a) Edema b) Eye sight reduce
	Nesvacumab ID: NCT02712008	Completed	a) During comparison with other anti-angiogenesis agent, no new safety signal observes.

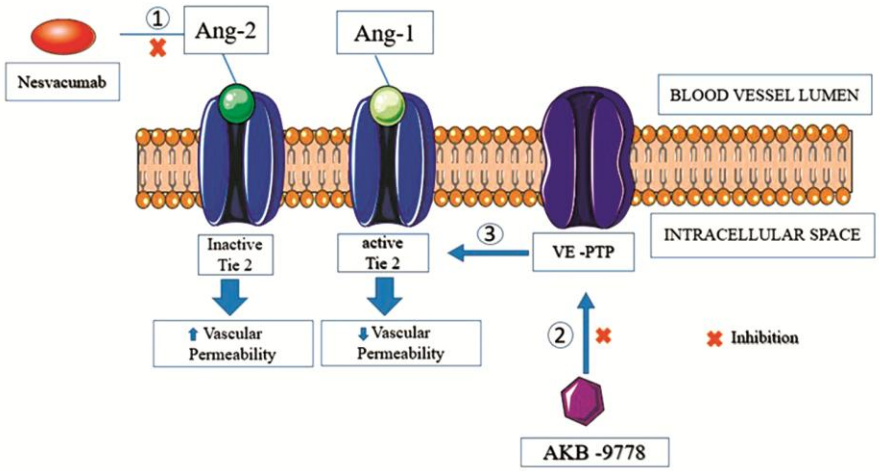

Fig. 6 — Nesvacumab blocks Ang-2, an antagonist of Tie2, to activate Tie-2 signaling and reduce vascular permeability. AKB-9778, a negative regulator of Tie-2 signaling, inhibits VE-PTP from activating Tie-2 signaling.

edema patients by blocking angiogenic factors (VEGF, PDGF, and b-FGF)[57]. Nesvacumab in combination with aflibercept is under clinical trial on patients with DME (clinicaltrials.gov ID: NCT02712008). Tie2 pathway, which is crucial in preserving vascular stability and integrity. Small molecule AKB-9778 promotes Tie2 and reduces vascular permeability because it blocks vascular endothelial-protein tyrosine phosphatase (VE-PTP), a negative modulator of Tie2[58]. An Ang-2 inhibitor called nesvacumab reduces vessel permeability by activating Tie2 (Fig. 6).

Anti-inflammatory agents

Intravitreal corticosteroid

In the treatment of DME, intravitreal steroids have become important, particularly in cases with resistant DME and DME that do not respond to anti-VEGF therapy[59]. To decrease capillary permeability and subsequently, DME, low quantities of corticosteroid may be administered into the eye. They exhibit a direct anti-inflammatory effect that is mediated by reducing the synthesis of pro-inflammatory cytokines, minimizing the expression of VEGF, the VEGF pathway downstream of the VEGF receptor, and the integrity and density of endothelial cell tight junctions to decrease retinal capillary permeability. Fluocinolone, triamcinolone, and dexamethasone (DEX) have been studied for the treatment of DME intravitreally[60].

Currently, the FDA-approved DEX and fluocinolone acetonide intravitreal implant. FA insert (0.2 mg) and unapproved triamcinolone acetonide are being utilized

as intravitreal steroids in clinical trials for DME. The DEX delivery system's effectiveness assures sustained medication exposure and significantly decreases the need for injections, which improves compliance among patients. The average number of injections for 3 years in the DEX implant trials (0.3 mg and 0.7 mg) in patients with DME was four. When compared to the sham group, DEX implant groups significantly reduced central retinal thickness (CRT) and improved BCVA. In the DEX implant group, more than 60% of patients experienced adverse events associated with cataracts. In an 18-month trial, individuals with refractory DME who received the DEX implant (0.7 mg) had considerably better BCVA and less CRT[61,62].

Insert FA is developed to treat DME. It has been evaluated in two different models, each of which produces FA at 0.23 and 0.45 g per day, respectively. In a 2-year trial, a single injection effectively raised BCVA in individuals with chronic DME. Currently, the FDA has approved the 0.23-g/day insert, which is associated with a considerably low incidence of ocular hypertension[63] (Table 2).

Non-steroidal anti-inflammatory therapy

Interleukin-6 (IL-6) has been explored as a potential target for anti-inflammatory treatment for DME since it is one of the most significant pro-inflammatory cytokines found in the vitreous of DR individuals, and it plays an important role in the pathogenesis of retinopathy[64]. Studies were conducted to determine the effectiveness and safety of interleukin-6 inhibitors like tocilizumab and EBI-031 in DME patients, but it has been withdrawn due to lost funding from sponsors.

Laser therapy

Traditional Laser Therapy

Before the introduction of anti-angiogenic treatment, laser photocoagulation was the standard for treating both PDR and DME. Early Treatment DR Study (ETDRS), a 22-month study, demonstrated that argon laser photocoagulation treatment significantly decreased macula edema and cut the probability of moderate vision loss by 50%[65]. The risk of severe vision loss has been significantly decreased by pan-retinal photocoagulation (PRP), particularly among PDR with a high risk of vitreous hemorrhage[66]. The exact mechanism behind how laser treatment lowers DME and causes neovascularization to reverse is not known, but it is assumed that direct sealing of leaky microaneurysms, a reduction in retinal blood flow that results in less retinal tissue and enhanced oxygenation, and promotion of the retinal pigment epithelium (RPE)[67,68]. Laser therapy continues to be a crucial adjuvant or rescue therapy, even though anti-VEGF therapy is currently taking the lead in DR treatment. When used as an adjuvant therapy, focused laser significantly decreased the need for anti-VEGF injections. Compared to DME patients receive just anti-VEGF therapy[69].

Novel Laser Approaches

To minimize adverse effects, attempts are also being undertaken to create novel laser techniques for the management of PDR and DME. A novel laser technique called PASCAL (Pattern scanning laser) is employed. By allowing for more accurate laser control and shorter treatment times, it minimizes laser-induced retinal damage[70]. To make it easier to deliver subthreshold burns and reduce collateral damage, micropulse methods like subthreshold micropulse diode laser (D-MPL) are currently used[71]. Recently, the use of NAVILAS (navigated laser system) boosted the accuracy of laser spots given to the retina and created favorable optical outcomes[72].

Miscellaneous agents

Cardiolipin inhibitor

A special phospholipid called cardiolipin is biosynthesized mainly at the inner level of the

Table 2 — Intravitreal steroids and non-steroidal anti-inflammatory drugs

Class	Drug	Status	Adverse Effects
Intravitreal Steroid	DEX implant	FDA approved	Cataract Elevation in intraocular pressure Vitreous hemorrhage
	FA insert	FDA approved	Cataract Ocular hypertension Glaucoma
IL-6 receptor inhibitor	Tocilizumab	Clinical trial Phase II (ID: NCT02511067)	Withdrawn
IL-6 inhibitor	EBI-031	Clinical trial Phase I (ID: NCT02842541)	Withdrawn

mitochondrial membrane[73]. The functions of phospholipids play multiple roles in biological membranes. Due to oxygen radical bombardment, phospholipids may experience oxidative damage in their acyl chains, which could be involved in cell death[74]. By reducing mitochondrial oxidative stress, peptides that target cardiolipins specifically, MTP-131, demonstrated a positive impact on eyesight in diabetic mouse models[75]. The clinical effectiveness of MTP-131 (OcuviaTM) ophthalmic topical solution in DME individuals has completed the phase-II study (clinicaltrials.gov ID: NCT02314299).

Cibinetide

It is also known as ARA 290 and helix B surface peptide (HBSP). It is a small peptide that is produced from erythropoietin (EPO). Having significant anti-apoptotic, anti-inflammatory, and anti-permeability properties[76]. Study shows that treatment with an EPO-derived peptide can significantly protect against neuroglial and vascular degenerative pathology without changing hematocrit or worsening neovascularization. These discoveries have implications for treating conditions like DR[77]. Phase 2 clinical trial is now being conducted to determine the efficacy of cibinetide in the treatment of DME.

Lipoprotein-Associated Phospholipase A2 Inhibitor

Lipoprotein-associated phospholipase A2 (Lp-PLA2) is responsible for the hydrolysis of oxidized Low-density lipoproteins, generating proinflammatory by-products that may impair vascular function and depletion of BRB during DR[78]. In 3 months, phase IIa clinical trial (ClinicalTrials.gov Identifier: NCT01506895) in treatment for DME, darapladib, a particular Lp-PLA2 inhibitor, revealed substantial reductions in macular edema and improved BCVA[79].

Aldose reductase inhibitors (ARIs)

The first ARI to go through clinical trials, sorbinil, failed to have much of an impact on DR onset or progression[80]. Numerous ARIs that were developed in the last 20 years, such as tolrestat, lidorestat, and zenarestat, have been discovered to be toxic to the liver and kidneys. Greater safety profiles for ponalrestat and zopolrestat also revealed greater potency. Clinical trials, however, only showed a small effect, possibly because the pathway was not sufficiently inhibited. A novel ARI, ARI-809, is more potent, has a high selectivity for aldose reductase, and has shown a positive effect in studies[81].

Protein kinase C (PKC) inhibitors

Certain specific PKC isoform inhibitors will be able to prevent the development of diabetes-related vascular and ocular pathology. PKC412—one of the first PKC inhibitors—reduced the effects on multiple PKC isoforms and improved visual acuity when given orally (100 mg/d) to individuals with DME[82]. Studies on the selective inhibition of PKC-b by ruboxistaurin mesylate are being conducted because the isoform PKC-b is highly expressed in the diabetic retina, and these studies have shown positive results in DR animal models[83,84] (Table 3).

NF-kB Inhibitors

The use of dehydroxymethyl-epoxyquinomicin, an NF-kB inhibitor. It has been demonstrated that it inhibits tumor development and angiogenesis in vivo as well as cytokine expression in vitro. In a different research, NF-kB inhibition caused the VEGF and ICAM-1 levels in the diabetic retina to be suppressed; this approach might enable future novel therapies to prevent the onset and early treatment of DR[85].

Artificial Intelligence tools in retinopathy

The future treatment for DR is steadily evolving forward including technologies such as artificial intelligence (AI) and machine learning, and novel formulations with more specific targeted drug delivery systems and sustained-release products. The usage of AI has been widened in the medical field a lot. AI is playing a transformative role in the diagnosis, management, and treatment of diabetic retinopathy (DR). Mainly, deep learning has enabled more accuracy and efficiency in identifying retinopathy. AI excels in the early detection of DR by analyzing retinal images such as fundus photographs or Optical Coherence Tomography (OCT) scans[86]. Deep learning models are trained on large datasets of interpreted images to identify microaneurysms, blood vessel damage, hemorrhages, and exudates. These models can rate the severity of DR, aiding clinicians in deciding and initiating fast treatment. AI-powered tools are being increasingly used in screening programs, particularly in areas with limited access to ophthalmologists. In risk prediction and proactive care, AI systems can analyze a patient's medical history, including blood glucose levels and blood pressure, to predict their risk of developing DR[87]. AI applications like IDx-DR, an FDA-approved system, and DeepMind's AI (Google Health) are already making waves. IDx-DR autonomously screens for

Table 3 — Summary of Oral and Injectable Agents under clinical investigation for DR.

Category	Agent	Type	Mechanism of Action	Clinical Trial Phase / Status
Oral Agents	RZ402	Oral PKal inhibitor	Reduces kallikrein–kinin–mediated vascular permeability	Phase 2 Completed (NCT05712720)
	PER-001	Oral PKal inhibitor	Blocks inflammatory/vascular leakage pathways	Phase 2 Active, Not recruiting (NCT06003751)
	YD-312	Oral antioxidant/anti-inflammatory	Targets oxidative stress–related retinal damage	Phase 2 (Asia) Unknown status (NCT03635814)
	Fenofibrate	PPAR-α agonist	Reduces inflammation and microvascular injury	FIELD & ACCORD-Eye trials Completed[104,105]
	APX3330	Oral Ref-1 inhibitor	Inhibits angiogenesis + inflammation	Phase 2 Completed NCT04692688
Injectable Agents	Faricimab	Intravitreal bispecific Ab	Dual VEGF-A & Ang-2 blockade	Phase 3 (YOSEMITE NCT03622580 /RHINE NCT03622593)
	KSI-301 (Tarcocimab)	Anti-VEGF (ABC platform)	Long-acting VEGF suppression	Phase 3 Terminated (NCT05066230)
	RGX-314	AAV8 gene therapy	Long-term anti-VEGF expression	Phase 2 Active, Not recruiting (NCT04567550)

DR, while DeepMind's AI is capable of diagnosing DR and other eye diseases from retinal scans with accuracy comparable to human experts[88].

Gene therapy

The medical field is also shifting towards personalized medicine and gene therapy, which can be useful in designing treatments according to the different patients. Stem cell therapies are promising for restoring vision in advanced DR cases. Research into retinal cell transplantation and CRISPR gene editing may provide curative solutions for irreversible damage[89]. Gene research and adaptation to newer technological treatments for DR will reduce the adverse effects caused by older therapies and decrease the overall percentage of vision loss.

Future Directions

Future therapies for diabetic retinopathy are shifting toward long-lasting, personalized, and less invasive approaches. Sustained drug-delivery systems—including biodegradable implants, refillable reservoirs, and targeted nanoparticles aim to reduce treatment burden while maintaining therapeutic effect[90,91]. Gene therapies using AAV vectors for durable VEGF and cytokine suppression, along with CRISPR-based editing of pro-angiogenic genes, are advancing toward clinical translation[92,93]. Non-invasive strategies such as topical nano-formulations capable of retinal penetration and trans-scleral iontophoresis have shown encouraging preclinical outcomes[94,95]. Artificial intelligence will further enhance DR care by enabling predictive risk modeling, automated referral pathways, and home-based retinal imaging[96,97]. Regenerative and neuroprotective modalities, including stem-cell-derived RPE transplantation and peptides like cibinetide (ARA290), represent promising avenues to restore retinal integrity and limit neurode-generation[98,99]. Effective screening is critically important for preventing vision loss in DR however, patient compliance remains suboptimal due to several common reasons such as missed or delayed screening due to limited awareness of DR progression, the misconception that screening is unnecessary in the absence of symptoms, financial constraints, reduced accessibility to screening centres, and overall poor health literacy issues that are particularly prominent in underserved populations[100]. Artificial intelligence offers a promising opportunity to address these challenges by enabling automated, point-of-care DR detection with high diagnostic accuracy. FDA-approved autonomous AI diagnostic systems (NCT02963441) have demonstrated real-world feasibility for DR detection without specialist involvement, substantially improving access to screening services[101]. Deep-learning models further enhance the ability to identify referable DR and can be deployed across community clinics, primary care settings, and tele-ophthalmology networks to optimize referral pathways and minimize missed

diagnoses[102,103]. By integrating predictive analytics, automated risk stratification, and portable image-capture technologies, AI-driven screening workflows can significantly improve patient uptake, reduce geographic and economic disparities, and distance, ultimately reduce preventable vision loss among individuals with diabetes.

Conclusions

The pathophysiology of DR is associated with many interdependent mechanisms, and many pathways are linked with diabetes-associated retinopathy. Treatment options for DR include laser treatment, vitrectomy, or medication. However, these treatments and techniques either lead to mild discomfort or systemic side effects. This review covers the current as well as novel therapeutic targets and antidiabetic medicines that are beneficial in the management of DR. Exploring novel therapeutic approaches and antidiabetic medications could be key in advancing the management of DR. Research into new treatment modalities that target specific pathways implicated in the disease progression could potentially offer more effective and less invasive options for patients. Continued research and development in this field are crucial to improving outcomes for individuals affected by DR, ultimately enhancing their quality of life and reducing the burden of this sight-threatening complication of diabetes.

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