Review

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Advances in the Molecular Pathophysiology and Emerging Therapeutic Strategies for Diabetic Retinopathy

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Abstract

Diabetic retinopathy (DR) is a major microvascular complication of diabetes and a leading cause of vision loss in working-age adults worldwide. The pathophysiology of DR is complex and involves oxidative stress, inflammation, retinal pigment epithelium (RPE) dysfunction, and abnormal angiogenesis. Recent insights into the molecular mechanisms underlying DR have opened new avenues for targeted and personalized therapeutic strategies. In this review, we examine the advances in the understanding of oxidative damage, RPE impairment, and proangiogenic signaling in DR progression. We also highlight emerging treatment modalities, including anti-VEGF agents, gene therapy, and nutraceutical interventions. Future directions emphasize the integration of omics technologies and precision medicine approaches for individualized management. This work provides a critical synthesis of recent findings and identifies promising avenues for research and clinical intervention in DR.

Keywords: diabetic retinopathy; oxidative stress; angiogenesis; retinal pigment epithelium; precision medicine; targeted therapy

1. Diabetic Retinopathy (DR)

Current worldwide estimations show that near to 463 million of adults suffer from diabetes, with a projected increased prevalence of 693 million by 2045, making it a condition of serious public health concern [1,2]. Prevalences of children and adolescents with diabetes have been increasing, with estimations of more than one million children and adolescents below 20 years diagnosed with type 1 diabetes [2].

Diabetes is one of the top 10 leading causes of global death, that negatively affects improvements in life expectancy [3]. There is evidence that shows that diabetes is associated with an increased mortality from infections, cardiovascular disease, stroke, chronic kidney disease, chronic liver disease, and cancer [3–6].

Diabetes is a chronic condition characterized by high levels of glucose in blood, due to insulin production that could be non-existent, insufficient or wrongly utilized [7]. In addition to hyperglycemia, diabetes may be accompanied by dyslipidemia and neurovascular damage [7,8].

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Hyperglycemia effects may develop microvascular (that includes retinopathy, nephropathy, and neuropathy) and macrovascular complications (that involves ischemic heart disease, peripheral vascular disease, and cerebrovascular disease) [9]. Increases in protein glycation can affect tissues, in diabetic retinopathy, this process generates apoptosis of retinal pericytes, overproduction of endothelial growth factors, increased neovascularization, and vascular inflammation, contributing to an elevated risk of microthrombosis formation, capillary blockage, and retinal ischemia [10].

One of the most common microvascular complications is diabetic retinopathy, which affects nearly 103 million of adult population with diabetes, and has a predicted increased prevalence of 160 million by 2045 [1].

Diabetic retinopathy is a chronic, progressive, and multifactorial disease affecting the retinal microvasculature. **Figure 1** shows the molecular pathways in DR.

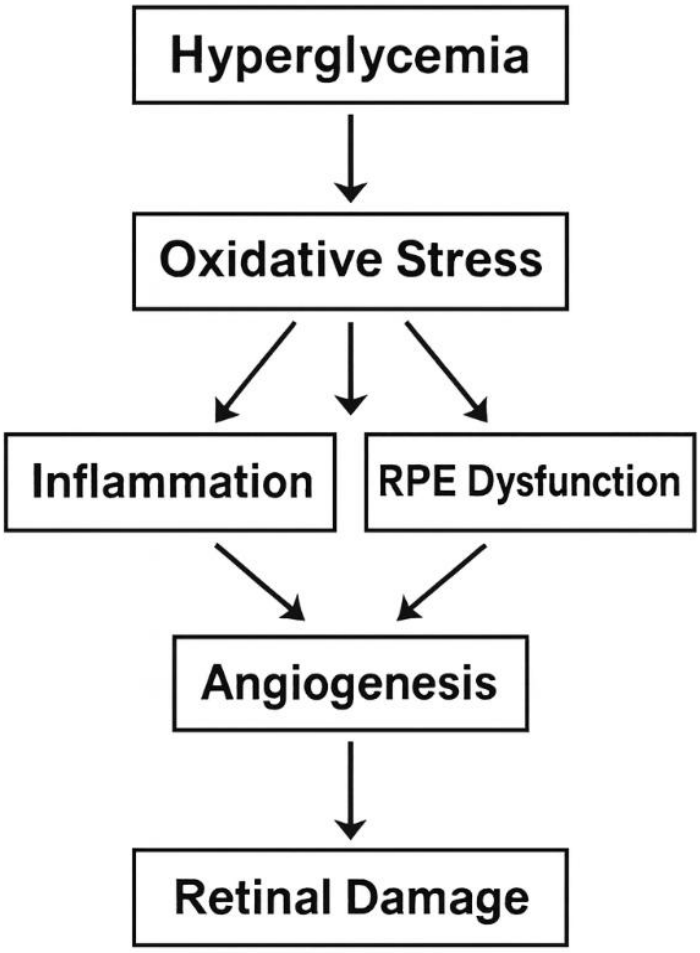

Figure 1. Molecular Pathways in Diabetic Retinopathy. Schematic representation of interconnected molecular mechanisms involved in DR pathogenesis: hyperglycemia induces oxidative stress, which contributes to retinal pigment epithelium (RPE) dysfunction, inflammation, and angiogenesis, ultimately leading to retinal damage and vision loss. (Adapted from Kowluru et al., 2007; Tang & Kern, 2011).

Hyperglycemia-induced metabolic disturbances lead to pericyte loss, endothelial dysfunction, and blood-retinal barrier (BRB) breakdown, ultimately resulting in retinal ischemia and neovascularization [11]. Retinal lesions, that are used to classify eyes as having one of the conditions in the categories of DR, are microaneurysms (small balloon-like bulges or tiny dots in the blood vessels in the retina), hemorrhages, venous beading (dilation and constriction of venular walls, resulting in changes of venous caliber), intraretinal microvascular abnormalities, hard exudates

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(yellow-white deposits, composed by leaked lipids and lipoproteins from the blood vessels), and retinal neovascularization (abnormal growing of new, often fragile, blood vessels that may be prone to bleeding) [12–15]. Diabetic retinopathy can be broadly categorized into non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) stages, with diabetic macular edema (DME) being a significant cause of visual impairment in both [13].

Non-proliferative diabetic retinopathy consists in the presence of many usual DR lesions, with the absence of neovascularization. This condition includes different stages, where the eyes can progress from no DR through mild, moderate and severe NPDR. Proliferative Diabetic Retinopathy is the most advanced stage of DR, characterized by the presence of neovascularization, and considered an angiogenic response to the reduction or interruption of blood flow of retina blood vessels [13]. The most common classification system for DR is the International Classification of DR scale [16], that locates the different stages of NPDR and PDR (**Table 1**).

Table 1. Stages and Clinical Features of Diabetic Retinopathy. Summary of progression stages, characteristic features, typical fundus findings, and associated visual impairments. (Adapted from Schmidt-Erfurth et al., 2017.).

Stage	Key Features	Fundus Findings	Visual Impact
Non-Proliferative (NPDR)	Microaneurysms, dot hemorrhages	Cotton wool spots, hard exudates	Mild to moderate
Proliferative (PDR)	Neovascularization	Vitreous hemorrhage, retinal detachment	Severe vision loss
Diabetic Macular Edema (DME)	Retinal thickening in macula	Cystoid spaces in OCT	Blurred central vision

An optimal identification of DR severity stages is crucial to predict the risk of worsening DR and visual loss risk, and thus helps by giving directions to determine an appropriate referral, follow-up and treatment recommendations [13,17,18]. Usual recommendations on eye examinations for people diagnosed with type 2 diabetes without DR consist of an initial examination at the time of type 2 diabetes diagnosis, followed by an annual dilated eye examination. For people with type 1 diabetes diagnosis without DR, eyes should be initially examined five years after type 1 diabetes diagnosis and must have yearly ophthalmic examination [17].

2. Diabetic Retinopathy in the Context of Other Eye Diseases

The growing global burden of diabetes mellitus (DM) as the population ages is accompanied by a high prevalence of not only diabetic retinopathy (DR), but also other eye diseases associated with pathology of internal organs [19,20]. At the same time, although DR is the most specific complication of chronic hyperglycemia, people with DM may experience other eye diseases associated with this pathology such as cataracts, glaucoma, age-related macular degeneration (AMD), retinal vascular occlusion, and acute ischemic optic neuropathy, which collectively impairs vision in people with DM. especially in old age [21].

Based on the literature data, cataracts, glaucoma, age-related macular degeneration (AMD), etc. are among the main causes of visual impairment worldwide [20]. The question of whether there is a link between diabetes and most eye diseases has been the subject of controversy in the past, when little attention was paid to the general aging of mankind [22]. In the current situation, due to the aging of the population, diabetic patients began to develop age-related eye diseases more often, leading to visual impairment, while previously they died prematurely from cardiovascular complications [23]. In addition, the latest technological and therapeutic innovations both in the field of diabetes treatment and in ophthalmology require updating existing knowledge about the eye condition in patients with diabetes. Currently, there is no doubt that diabetes itself and long-term chronic hyperglycemia, against the background of sharp fluctuations in glucose levels, initiates the manifestation of numerous eye diseases (**Table 2**).

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Table 2. Diabetic retinopathy in the context of other eye diseases.

Diagnosis	Frequency of occurrence in patients with diabetes	Association with chronic hyperglycemia	The main pathogenetic mechanisms Associated diseases and conditions	Associated diseases and conditions
Diabetic retinopathy (DR)	The total frequency of occurrence is 20-25.7%. In patients with type 1 diabetes, 54.4%, in patients with type 2 diabetes [1,80].	A decrease in blood glucose by 10 mg/dl is directly related to a decrease in intraocular pressure by 0.09 mmHg [20].	Oxidative stress. Dysfunction of the retinal pigment epithelium. Abnormal angiogenesis. Inflammation of the retina. Disruption of neurotransmitter production. Violation of the production of trophic factors in the retina. Similar genetic correlations with OTHER dysbiosis of the ocular and intestinal microbiota [26,80–82].	Fatness. Cardiovascular diseases. Dyslipidemia. Atherosclerosis. Non-alcoholic fatty liver disease. Chronic kidney disease. Old age Intestinal diseases [27,83,84].
Cataract	Prevalence: 3.3% vs. 1.9% in patients with diabetes compared to the control group. The incidence of cataracts in people with diabetes is 3-5 times higher than in healthy people. Up to 20% of all cataract surgeries are performed in patients with diabetes mellitus [85].	The risk of developing cataracts depends on the duration of diabetes and the severity of hyperglycemia [85].	Metabolic disorders Oxidative stress Old age Denaturation of lens proteins Dyslipidemia Smoking Similar genetic correlations with others) [26,81,86,87].	Obesity and metabolic syndrome. Old age. Cardiovascular diseases. High degree of myopia. Smoking. Exposure to sunlight. Therapy with steroids. Local injuries) Intestinal diseases [26,86,88–90]
Glaucoma	DR is the main cause of glaucoma, accounting for 30% to 52.38% of cases. glaucoma [22,87].	The probable risk of glaucoma in patients with chronic hyperglycemia is high [22,87].	Similar genetic correlations with others. Degeneration of axons. Neuroinflammation. Transynaptic degeneration of retinal ganglion cells. Dysbiosis of ocular and intestinal microbiota [22,82].	Old age. Systemic diseases Cardiovascular diseases [87].
Age-related macular degeneration (AMD)	Ambiguous results: The same prevalence or risk of developing DR or its progression. The number of people living with diabetes and AMD, DR is expected to grow rapidly due	High risk of developing DR with chronic hyperglycemia for more than 5 years [26].	Abnormal angiogenesis Inflammation Dyslipidemia Similar genetic correlations with others. Dysbiosis of the ocular and intestinal microbiota. [26,81,82].	Old age Cardiovascular diseases Fatness Intestinal diseases [26,82].

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	to the aging population and the additional risk of visual impairment outside of DR [20,26].			
Dry eye syndrome	Higher prevalence from 20% to 53% in patients with diabetes and others compared to the general population [91,92].	High risk in uncontrolled diabetes [92].	Similar genetic correlations with others. Instability of the tear film. Hyperosmolarity. Chronic inflammation. Violation of the production of tear proteins. Structural abnormality in the corneal nerve fibers. Autonomic neuropathy [93,94].	Old age Fatness Encephalopathy Cardiovascular diseases [92,95].

Thus, prolonged hyperglycemia promotes the accumulation of reactive oxygen species and reduces the antioxidant function of the aging retina, thereby accelerating the development of other diseases. Aging also causes mitochondrial dysfunction, which in turn contributes to the accumulation of reactive oxygen species, followed by apoptosis of trabecular meshwork cells. These processes increase the resistance to the outflow of intraocular fluid, which leads to a pathological increase in intraocular pressure and the development of glaucoma.

At the same time, the combination of aging and inflammation factors is accompanied by destabilization of the tear film, making it hyperosmotic and triggering a vicious cycle of inflammation in dry eye syndrome, which exacerbates the course of the disease [19]. Inhibitors or drugs that affect these processes, such as aldose reductase inhibitors, antioxidants, natural flavonoid compounds, and nanotechnology-based drugs, show promising prospects in the prevention and treatment of diabetic cataracts [24].

Early detection and correction of metabolic and inflammatory factors can also contribute to the development of effective strategies for the prevention of cataract development in the elderly. A Wisconsin epidemiological study by Dr. showed that the 10-year risk of developing cataracts ranges from 8.3% to 24.8% in type 1 and type 2 diabetics, respectively [23].

Aging causes mitochondrial dysfunction, which in turn contributes to the accumulation of reactive oxygen species, causing apoptosis of trabecular meshwork cells. These processes increase the resistance to the outflow of intraocular fluid, which leads to a pathological increase in intraocular pressure and the development of glaucoma. Thus, elderly people who control diabetes are significantly less likely to develop glaucoma, DR, or AMD than those who have not been diagnosed or controlled with diabetes [25]. In the English study, patients with controlled diabetes had a 1.29-fold higher adjusted chance of developing glaucoma (95% CI 1.01-1.65) than those without diabetes. The adjusted odds of developing diabetic eye disease were 1.20 times higher (95% CI 1.00-1.45) in individuals with uncontrolled DM; and the adjusted odds of developing AMD were 1.38 times higher (95% CI 1.04 -1.82) among individuals with undiagnosed DM [19].

Noteworthy are works demonstrating a common genetic correlation between DR, AMD, glaucoma, retinal detachment, and myopia. The revealed genetic correlation of common single nucleotide polymorphisms characterizes the significant commonality of the genetic structure of these diseases and their genetic relationship between AMD, DR, and glaucoma [26].

Studies conducted in recent years confirm the existence of a correlation between the gut, microbiota, and eyes, suggesting the concept of the "gut-eye" axis, which is involved in the pathogenesis of major eye diseases, including AMD, uveitis, etc., dry eye syndrome, and glaucoma [27].

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Thus, eye diseases can have common clinical symptoms and epidemiological comorbidity and simultaneously cause age-related macular degeneration (AMD), glaucoma, and diabetic retinopathy (DR) [28].

Based on the conducted studies, it can be assumed that the presence of common pathogenetic mechanisms in the most common eye diseases, such as inflammation, genetic correlations, dysbiosis, abnormal angiogenesis, gives grounds to express an opinion on the possibility of general preventive and therapeutic measures that can prevent or slow down the occurrence and progression of a common pathology. In this regard, there is an assumption about the possibility of introducing the term "chronic eye disease" if the patient has a combined pathology in the elderly and senile, especially since there is already a similar precedent in clinical medicine as "chronic kidney disease". This will make it possible to quickly and fully utilize all the advantages of comprehensive prevention and treatment of combined eye pathology, especially in the elderly with a wide range of somatic pathologies, including diseases of the cardiovascular system, digestive organs, and systemic pathology, including diseases directly or indirectly related to metabolic syndrome.

3. Oxidative Stress

Oxidative stress is a central contributor to DR pathogenesis (**Figure 2**). Oxidative stress is the reduced capacity of human body to neutralize the imbalanced production of reactive oxygen species (ROS), which are damaging molecules. ROS can harm the tissues in and around the retinal blood vessels, promoting the development of DR. It has been stablished that four key metabolic disturbances are linked to oxidative stress caused by hyperglycemia in the retina: the activation of the protein kinase C (PKC) signaling pathway, increased activity in the polyol pathway, stimulation of the hexosamine pathway, and formation of advanced glycation end products (AGEs) inside cells [29].

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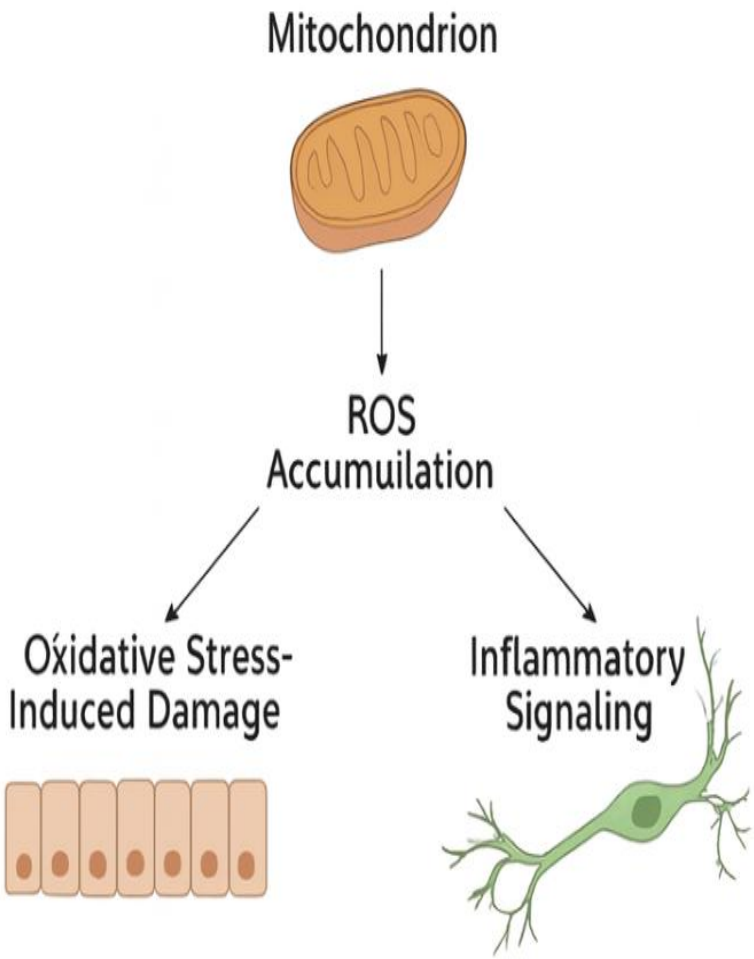

Figure 2. Oxidative Damage in Retinal Cells. Illustration of oxidative stress-induced damage in retinal pigment epithelium and neuronal cells, including mitochondrial dysfunction, ROS accumulation, and inflammatory signaling. (Adapted from Madsen-Bouterse & Kowluru, 2008).

Chronic hyperglycemia enhances mitochondrial superoxide production, triggering downstream pro-inflammatory and pro-apoptotic pathways [30]. Reactive oxygen species (ROS) activate the NF-κB pathway, increase cytokine release (e.g., IL-1β, TNF-α), and disrupt tight junctions in retinal endothelial cells [31]. NADPH oxidase (NOX) enzymes and advanced glycation end-products (AGEs) also amplify oxidative damage, creating a vicious cycle of cellular injury [32].

4. Retinal Pigment Epithelium (RPE)

Although traditionally associated with outer retina function, RPE cells are increasingly recognized as active participants in DR. Hyperglycemia induces oxidative damage and mitochondrial dysfunction in RPE cells, leading to impaired phagocytosis of photoreceptor outer segments and increased secretion of angiogenic factors such as VEGF [33]. RPE dysfunction disrupts the outer BRB and facilitates photoreceptor degeneration.

5. Angiogenesis

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Angiogenesis in DR is predominantly driven by hypoxia-induced overexpression of vascular endothelial growth factor (VEGF). This growth factor increases vascular permeability and promotes neovascularization [34], which characterizes PDR. The HIF-1α/VEGF axis is a major therapeutic target. Anti-VEGF agents (e.g., ranibizumab, aflibercept, bevacizumab) are now first-line treatments for DME and PDR [35,36]. However, incomplete responses and resistance highlight the need for alternative angiogenic modulators like angiopoietin-2 inhibitors and integrin antagonists [37]. In addition to VEGF, there are other angiogenic factors such as platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF). Platelet-derived growth factors comprise a group of signaling proteins that regulate cell proliferation and tissue growth. Upon activation, platelets, smooth muscle cells, endothelial cells, and activated macrophages release PDGFs, which play essential roles in embryonic vasculogenesis and in directing mesenchymal cell migration, proliferation, and chemotaxis [38]. There is evidence in animal models that shows increased retinal angiogenesis due to augmented levels of PDGF-BB in diabetic retinal cells [39]. Fibroblast growth factors involves 23 members of a family (FGF 1-23) that have a crucial role on the regulation of metabolic balance and cell biological processes related to some chronic diseases, such as diabetes, obesity, chronic kidney disease, cancer, among others [40]. In DR, FGF-16 is involved in the regulation of high glucose-induced glomerular endothelial cell dysfunction and cell proliferation [41,42].

6. Current Treatment of DR

Laser Treatment: Panretinal photocoagulation (PRP) is the most widely employed conventional laser therapy for diabetic retinopathy, with well-established long-term efficacy in preserving retinal and choroidal neurovascular integrity [43].The therapeutic effect of retinal laser treatment is based on the induction of thermal damage and protein denaturation in pigment-containing target tissues via light absorption, leading to permanent chorioretinal scarring whose extent and healing dynamics are determined by the intensity of the applied laser energy.

Retinal laser photocoagulation primarily exerts its therapeutic effect by reducing photoreceptor-mediated oxygen consumption, thereby increasing oxygen diffusion from the choriocapillaris through glial scarring to the inner retina, which alleviates hypoxia, downregulates vasoactive mediators such as VEGF and PKC, inhibits neovascularization, reduces capillary hydrostatic pressure and retinal edema, and facilitates direct choroidal oxygen delivery [44,45].

A secondary proposed mechanism of retinal laser photocoagulation suggests that the therapy reduces levels of pro-angiogenic stimuli by selectively ablating cells involved in neovascular signaling, while concurrently promoting the release of anti-angiogenic factors (like TGF-β, EPO, and PEDF) from the scar tissue formed during retinal repair [46–48]. Additionally, conventional focal laser treatment for retinal edema is thought to seal leaking microaneurysms, thereby limiting cytokine-mediated inflammation and facilitating macular edema reabsorption, whereas grid laser photocoagulation may alleviate macular edema by enhancing retinal oxygenation, relieving hypoxia, and inducing retinal artery dilation through decreased autoregulatory tone [48].

Long-term use of conventional laser photocoagulation has been associated with significant adverse effects, including permanent retinal scarring, iatrogenic macular edema from excessive thermal injury, choroidal detachment, peripheral visual field loss, delayed dark adaptation, and atrophic creep [49]; to address these limitations, modern laser systems have introduced refinements in pulse duration, wavelength, and spot size to improve precision and safety [50–52].

Technological advancements have led to the development of various clinical laser and delivery platforms aimed at enhancing the precision and safety of retinal therapies. Endpoint management algorithms now allow for fine-tuned control of laser energy relative to titration thresholds, enabling delivery of subvisible retinal burns with high accuracy [53]. Additionally, image-guided systems, such as navigational lasers, integrate fundus imaging with laser delivery devices to facilitate highly targeted and predetermined photocoagulation, particularly in the treatment of diabetic macular edema [54].

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Despite the widespread use of anti-VEGF and corticosteroid agents for DR and DME, laser photocoagulation remains a valuable therapeutic option due to its cost-effectiveness, durability, and reduced dependency on frequent follow-up in real-world clinical settings. Conventional approaches such as PRP provide long-term efficacy and help prevent progression to vision-threatening complications like vitreous hemorrhage and neovascular glaucoma, while also decreasing the frequency of anti-VEGF injections in combined therapies [48]. However, conventional laser treatment (characterized by long pulse durations) can induce adverse effects including retinal scarring, subretinal fibrosis, inflammation, visual field loss, and transient VEGF upregulation, potentially exacerbating DME; these limitations highlight the need for combination regimens and further development of advanced laser platforms that minimize collateral damage and optimize visual outcomes [55].

Surgical Treatment: Vitrectomy is a key surgical intervention for managing advanced stages of DR, particularly in cases involving intravitreal hemorrhage or tractional and rhegmatogenous retinal detachment. The procedure involves removal of the vitreous gel, along with blood and fibrovascular membranes, to relieve retinal traction and inhibit vitreoretinal proliferation, ultimately aiming to preserve or stabilize visual function. In less complex cases, such as non-clearing vitreous hemorrhage with minimal fibrovascular proliferation and posterior vitreous detachment, a straightforward vitrectomy may suffice; however, more extensive pathology affecting the macula requires complex surgical planning and technique [56].

Over recent decades, vitrectomy techniques have evolved significantly, shifting from traditional 20G systems to minimally invasive 23/25/27G platforms equipped with 3D visualization and wide-angle viewing systems like Resight® [57–59]. These advances have allowed for smaller incisions, reduced surgical trauma, greater cutting efficiency, and improved intraoperative visualization, thereby enhancing safety and outcomes. Additionally, preoperative intravitreal administration of anti-VEGF agents in complex PDR cases has been shown to reduce intra and postoperative bleeding, decrease the need for intraoperative electrocoagulation, shorten operative time, and lower complication rates [60,61].

Despite these technological improvements, some patients still experience suboptimal visual recovery following vitrectomy. Membrane peeling can lead to intraoperative bleeding or iatrogenic retinal injury, and postoperative complications such as paracentral acute middle maculopathy, intraocular inflammation, neovascular glaucoma, and vitreous rebleeding may occur. Combining vitrectomy with intravitreal injections of anti-VEGF agents or corticosteroids has demonstrated potential in optimizing perioperative conditions, reducing retinal fibrosis, and minimizing postoperative complications, representing a promising strategy for improving overall surgical outcomes in DR patients [56,61–63].

In proliferative diabetic retinopathy, the posterior hyaloid membrane has a key role in the formation of fibrovascular membranes and the development of retinal traction and further - retinal detachment. Observational studies have shown that the cases with complete posterior vitreous detachment patients have a lower risk of neovascularization progression, while the preserved posterior hyaloid membrane contributes to traction and the growth of new vessels [64].

That suggests that vitrectomy in cases with early signs of proliferative activity may provide better functional results and reduce the incidence of severe complications compared to delayed surgical treatment. Induction and removal of the posterior hyaloid membrane in the early stages is considered a preventive measure that can reduce the risk of tractional detachment and the progression of PDR to advanced stages [65].

Intravitreal Corticosteroids: Corticoids exert broad anti-inflammatory effects by reducing vascular permeability, suppressing the transcription of pro-inflammatory cytokines, and modulating the activity of fibroblasts and endothelial cells, thereby limiting tissue edema and neovascular processes in inflammatory and ischemic retinal conditions [66]. Corticosteroids, particularly Intravitreal triamcinolone acetonide, has been utilized in the treatment of DME due to its strong anti-inflammatory and anti-angiogenic properties, with multiple randomized controlled trials reporting

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significant improvements in retinal thickness and visual acuity [67–69]. However, many of these studies were limited by small sample sizes and short follow-up durations, and the treatment has been associated with notable adverse effects, including increased intraocular pressure, cataract progression, and risk of intraocular infection [70].

Recent advances in sustained intraocular drug delivery have led to the development of intravitreal and retinal implants for DME, offering prolonged therapeutic effects [70]. In a randomized controlled trial, the surgically implanted fluocinolone acetonide device (Retisert) demonstrated significantly greater DME resolution and visual acuity improvement at 3 years compared to standard care; however, it was associated with high rates of cataract formation and glaucoma, with 5% of patients requiring implant removal [71].

Intravitreal Antiangiogenesis Agents: Vascular endothelial growth factor (VEGF), particularly the VEGF-A isoform, plays a central role in the pathophysiology of DR and DME by promoting endothelial cell proliferation, migration, vascular leakage, and pathological angiogenesis in hypoxic retinal tissues. VEGF-A is considered the most potent angiogenic factor among the VEGF family and is critically upregulated in response to retinal ischemia and hyperpermeability, making it a key therapeutic target in DR management [72–75].

Intravitreal anti-VEGF agents (including ranibizumab, aflibercept, and bevacizumab) have become first-line treatments for DME and proliferative DR due to their ability to inhibit abnormal neovascularization and reduce vascular leakage . Clinical trials have demonstrated their efficacy in improving visual acuity and reducing macular thickness. Pegaptanib, an agent targeting the VEGF165 isoform, showed significant visual and anatomical benefits in DME patients, with a low incidence of serious adverse events [76–78]. Similarly, ranibizumab and bevacizumab, originally developed for neovascular age-related macular degeneration (AMD), have shown promising results in DME and DR, with ongoing trials evaluating their comparative effectiveness and safety profiles [75].

Despite their clinical efficacy, concerns remain regarding systemic safety (particularly for off-label agents like bevacizumab) and the need for repeated intravitreal injections poses challenges in long-term disease management [79]. Combination therapies with laser photocoagulation are being explored to reduce injection frequency and improve outcomes. Overall, anti-VEGF therapy represents a cornerstone in the current treatment paradigm for DR and DME [70,75].

7. What Is Next for DR? Future Directions: Personalized Medicine and Targeted Therapies

With advancements in genomics, transcriptomics, and metabolomics, personalized medicine is emerging as a promising paradigm. Individual genetic variations (e.g., SNPs in VEGF, RAGE, and HIF1A genes) influence DR susceptibility and treatment response [38]. Precision diagnostics and molecular profiling may soon allow clinicians to stratify patients and tailor interventions based on individual risk signatures. Epigenetic regulators (miRNAs, lncRNAs) are also being explored as biomarkers and therapeutic targets.

The future of diabetic retinopathy (DR) management is moving rapidly toward personalized medicine, driven by advances in genomics, transcriptomics, proteomics, and metabolomics. Increasing evidence demonstrates that individual genetic and epigenetic variations significantly modulate susceptibility to DR and response to therapies (**Table 3**).

Table 3. Current and Emerging Therapies for Diabetic Retinopathy. Comparison of therapies based on targets, mechanisms of action, and clinical development stage. (Adapted from Boye et al., 2014; Dugel et al., 2020.).

Therapy	Target	Mechanism	Clinical Stage
Anti-VEGF (e.g., ranibizumab)	VEGF-A	Inhibits angiogenesis	Approved
Corticosteroids	Inflammation	Suppress cytokine release	Approved

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Antioxidants (e.g., lutein)	ROS	Reduces oxidative stress	Preclinical/Clinical
Gene therapy	VEGF, PEDF	Long-term suppression or overexpression	Experimental
Stem cell therapy	Retinal regeneration	Replaces damaged cells	Experimental

For example, single nucleotide polymorphisms (SNPs) in angiogenic and inflammatory genes such as VEGF-A, RAGE, and HIF1A influence both disease progression and therapeutic efficacy, while circulating epigenetic regulators—including microRNAs (miR-21, miR-126, miR-200b) and long non-coding RNAs (MALAT1, MIAT)—emerge as promising biomarkers and therapeutic targets [38,72,73]. Integrating these molecular signatures into precision diagnostics may allow clinicians to stratify patients into subgroups characterized by angiogenic, inflammatory, or oxidative stress profiles, enabling risk prediction and individualized therapy selection. Moreover, epigenetic modifications underpin the phenomenon of 'metabolic memory,' whereby prior poor glycemic control leaves long-lasting damage despite subsequent normalization, suggesting that early intervention guided by molecular profiling is essential for altering disease trajectories [29,30,38].

Parallel to these discoveries, the integration of multi-omics with artificial intelligence (AI) and machine learning is transforming predictive modeling in DR. AI-driven algorithms trained on retinal imaging, systemic metabolic data, and genetic profiles can detect subclinical disease, forecast progression, and identify likely responders to anti-VEGF or corticosteroid therapies with increasing precision [61,72,74]. Emerging 'digital twin' models simulate patient-specific disease trajectories, offering clinicians a powerful tool to design adaptive and personalized treatment plans [75]. At the therapeutic level, pharmacogenomics is clarifying interindividual variability in drug response, paving the way for genotype-guided dosing of anti-VEGF agents or corticosteroids [38,73]. Furthermore, innovations in drug delivery systems, such as nanotechnology-based carriers (liposomes, dendrimers, micelles) and long-acting gene therapies (AAV2-sFLT01 vectors), promise to enhance intraocular bioavailability, prolong therapeutic effect, and reduce injection burden [61,70]. Stem cell therapies, particularly induced pluripotent stem cell (iPSC)-derived retinal cells, also represent a regenerative frontier, offering potential for tissue replacement and restoration of neurovascular integrity in advanced disease [70,75].

Looking ahead, personalized nutraceutical and lifestyle-based strategies are expected to complement high-technology therapeutics. Nutrients such as lutein, zeaxanthin, resveratrol, curcumin, and omega-3 fatty acids have shown differential benefits depending on patient-specific oxidative stress and lipidomic profiles, suggesting that dietary and nutraceutical interventions could be tailored to molecular phenotypes [11,40,70]. Integration of wearable glucose sensors, continuous retinal imaging, and telemedicine platforms will further support individualized disease monitoring and real-time adaptation of therapy [8,19,75]. Nonetheless, significant challenges remain, including high costs, limited access to omics technologies in low-resource settings, and ethical concerns regarding data privacy and equitable distribution of precision treatments [72, 74]. Ultimately, the convergence of multi-omics, AI, regenerative medicine, and advanced drug delivery platforms has the potential to transform DR care into a truly personalized paradigm, reducing the global burden of blindness by delivering the right intervention to the right patient at the right time [38, 70, 75].

8. Targeted Therapies

The development of targeted therapies for diabetic retinopathy (DR) (**Figure 3**) represents a crucial step in overcom[72,74ing the limitations of conventional anti-VEGF treatments. Gene therapy has emerged as a particularly promising avenue, aiming to provide long-term suppression of pathogenic pathways through single or infrequent interventions. Adeno-associated viral (AAV) vectors, such as AAV2-sFLT01, deliver soluble VEGF receptors to neutralize VEGF activity and reduce neovascularization [38,70]. Early-phase clinical trials suggest that gene-based approaches can achieve sustained intraocular expression of therapeutic proteins, reducing the frequency of injections compared to conventional biologics [61]. Beyond VEGF blockade, ongoing research explores the

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delivery of genes that encode anti-inflammatory mediators, neuroprotective factors, or antioxidative enzymes, expanding the therapeutic landscape toward multi-targeted interventions [75].

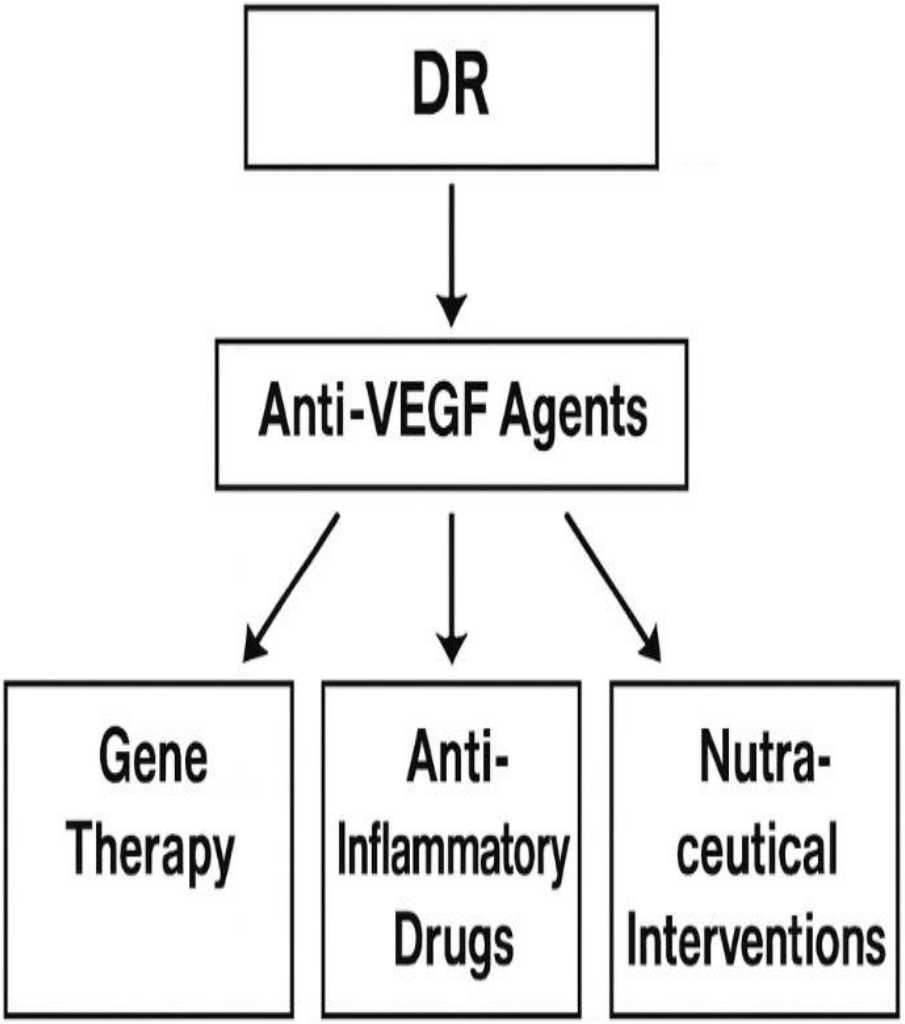

Figure 3. Therapeutic Targets in Diabetic Retinopathy. Overview of current and emerging therapeutic strategies, including anti-VEGF agents, antioxidants, anti-inflammatory drugs, gene therapy, and nutraceutical interventions. These targets aim to mitigate molecular alterations associated with DR. (Adapted from Sheikpranbabu et al., 2009; Ma et al., 2017).

In parallel, antioxidant therapies have garnered considerable interest, given the central role of oxidative stress in DR pathogenesis. Compounds such as resveratrol, curcumin, quercetin, and N-acetylcysteine (NAC) have demonstrated the ability to modulate redox homeostasis, inhibit mitochondrial dysfunction, and attenuate ROS-mediated inflammatory signaling [29,40]. Preclinical studies confirm that these molecules can prevent retinal endothelial apoptosis and pericyte loss, while clinical studies are beginning to validate their adjunctive use in DR patients with poor glycemic control [72]. The challenge remains in achieving sufficient intraocular bioavailability; thus, nano

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formulations of polyphenols and synthetic antioxidant mimetics are actively being investigated to enhance stability, penetration, and sustained release [61].

Anti-inflammatory strategies are equally important, as inflammation is a key driver of microvascular injury and neovascularization in DR. Therapeutics targeting cytokines such as IL-6, IL-1β, MCP-1, or signaling cascades like JAK/STAT and NF-κB have shown efficacy in reducing leukostasis, vascular leakage, and blood–retinal barrier breakdown [31,73]. Agents such as tocilizumab (IL-6R inhibitor) and novel small molecules targeting microglial activation are under clinical evaluation, offering potential alternatives or adjuncts to anti-VEGF monotherapy [74]. Importantly, combined inhibition of angiogenic and inflammatory pathways appears to yield superior outcomes, underscoring the need for multi-modal targeted therapy approaches.

Finally, nutraceutical and nanotechnology-based delivery systems are being increasingly recognized as promising complementary strategies. Nutrients such as lutein, zeaxanthin, omega-3 fatty acids, and vitamin D exhibit neuroprotective and anti-inflammatory effects, with evidence suggesting they can reduce oxidative damage in the retinal pigment epithelium and photoreceptors [11,70]. The challenge of ocular drug delivery, however, is compounded by the anatomical and physiological barriers of the eye, including the cornea, conjunctiva, sclera, blood–aqueous barrier (BAB), and blood–retinal barrier (BRB). Advances in nanotechnology—including liposomes, dendrimers, polymeric nanoparticles, and hydrogels—offer solutions to overcome these barriers, enabling controlled, targeted, and prolonged release of both small molecules and biologics [61,75]. Such innovations are expected to revolutionize the therapeutic management of DR, providing safer and more efficient alternatives to current intravitreal injection regimens.

9. Analysis of Key Findings in DR Research

Diabetic retinopathy (DR) is driven by a tightly interconnected triad of oxidative stress, inflammation, and aberrant angiogenesis. A robust body of evidence links systemic and intraocular oxidative stress markers with DR incidence, severity, and progression, including activation of mitochondrial ROS, hexosamine and polyol pathway flux, and AGE formation that perpetuate vascular injury [29–32]. These mechanisms promote pericyte apoptosis, endothelial dysfunction, and blood–retinal barrier (BRB) breakdown, providing a biologic rationale for antioxidant and redox-restoring strategies as adjuncts to standard care [29,30]. Concurrently, inflammatory signaling (e.g., NF-κB activation, leukostasis mediated by IL-1β, TNF-α) further amplifies microvascular damage and crosstalks with hypoxia-inducible pathways to upregulate VEGF, thereby closing the loop between oxidative injury and pathological angiogenesis [31,32,34].

Across randomized trials and real-world cohorts, intravitreal anti-VEGF agents (ranibizumab, aflibercept, and bevacizumab) consistently reduce macular edema, improve or stabilize vision, and suppress neovascularization in DME and proliferative DR [72–78]. Head-to-head and network syntheses generally show superior or at least non-inferior anatomic and functional outcomes with anti-VEGF compared with intravitreal corticosteroids, while avoiding steroid-related adverse events such as intraocular pressure rise and cataract progression [66–70,75]. Beyond anti-VEGF, biologics that target inflammatory mediators (e.g., anti-TNF agents such as infliximab) have been investigated off-label or in early studies, reflecting the recognized role of inflammation in DR and the potential to complement angiogenesis inhibition [73–75]. Importantly, perioperative use of intravitreal agents can improve surgical fields and outcomes in complex PDR—reducing intraoperative bleeding, operative time, and postoperative complications when used adjunctively with vitrectomy [60,61,75].

A rapidly advancing frontier involves molecular and extracellular vesicle biomarkers that enable minimally invasive disease monitoring and treatment stratification. Circulating and aqueous humor microRNAs (including those packaged within exosomes) mirror retinal pathophysiology and correlate with DR stages, offering promise as non-invasive indicators of activity and response to therapy [7,38]. In parallel, multi-omics signatures (genomic variants in VEGF pathways, inflammatory gene expression modules, metabolomic fingerprints) are being integrated with imaging biomarkers (OCT, ultra-widefield angiography) and artificial intelligence models to predict

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progression and forecast individual treatment response, ultimately informing precision-guided regimens [8,18,38,61,72].

Therapeutically, combination and sequencing strategies, like anti-VEGF with navigated or subthreshold laser, or anti-VEGF followed by corticosteroid rescue in partial responders, can reduce injection burden and improve anatomical durability in selected patients [48,70,75]. Emerging modalities, including sustained-delivery implants and gene-based anti-VEGF expression (e.g., AAV2-sFLT01), aim to deliver longer-lasting disease control, whereas nanotechnology platforms are being optimized to traverse ocular barriers and achieve targeted posterior-segment delivery with fewer administrations [61,70,75]. Collectively, these advances underscore a shift from a one-size-fits-all approach toward pathway-directed and patient-tailored therapy that addresses the heterogeneity of DR biology and clinical expression [38,70,75].

10. Conclusions

Diabetic retinopathy (DR) remains a major cause of preventable blindness worldwide, with pathogenesis driven by oxidative stress, retinal pigment epithelium (RPE) dysfunction, chronic inflammation, and pathological angiogenesis [29–34]. Current anti-VEGF therapies have revolutionized management of diabetic macular edema (DME) and proliferative DR, yet incomplete responses, injection burden, and variability among patients emphasize the need for multi-targeted approaches [72–75]. Evidence indicates that persistent mitochondrial ROS, advanced glycation end-products (AGEs), and NF-κB–mediated cytokine activation amplify vascular damage, highlighting the importance of complementary antioxidant and anti-inflammatory interventions [29–32].

Emerging innovations include gene therapy (e.g., AAV2-sFLT01) and sustained-delivery implants, which aim to reduce treatment frequency while maintaining efficacy [61,70,75]. Nanotechnology-based carriers further promise to overcome ocular barriers, achieving targeted posterior-segment drug release. In parallel, advances in multi-omics and artificial intelligence (AI) are reshaping risk prediction, integrating genomic variants, transcriptomic modules, and metabolomic profiles with imaging biomarkers to identify patients at highest risk and tailor treatment intensity [8,18,61,72]. Circulating exosomal microRNAs also offer minimally invasive biomarkers for real-time monitoring of disease activity and treatment response [7,38].

Future research must prioritize randomized trials and mechanistic studies that validate biomarker-guided therapy, evaluate combined antioxidant, anti-inflammatory, and anti-angiogenic regimens, and assess the durability of next-generation delivery systems. Importantly, strategies must address challenges of cost, accessibility, and equitable distribution to ensure broad clinical adoption [70,72–75]. By integrating targeted therapies with precision diagnostics, the field is advancing toward personalized, durable interventions capable of preserving vision and reducing the global burden of DR.

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