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Diabetic Retinopathy: Pathophysiology and Modern Therapeutic Strategies

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Abstract

Diabetic retinopathy (DR) is one of the most common and serious chronic complications of diabetes mellitus, representing the leading cause of vision loss among working-age adults. The disease results from prolonged hyperglycemia, which leads to damage of the retinal microvasculature, causing endothelial dysfunction, increased vascular permeability, ischemia, and subsequent pathological neovascularization. Two main stages of DR are distinguished — non-proliferative (NPDR) and proliferative (PDR) — reflecting the progressive severity of vascular alterations within the retina.

Early stages of the disease are often asymptomatic, making regular ophthalmic screening and advanced imaging techniques, such as optical coherence tomography (OCT) and fluorescein angiography, essential for early detection. Management of diabetic retinopathy includes both systemic metabolic control (maintaining optimal blood glucose, blood pressure, and lipid levels) and local treatments, such as laser photocoagulation, intravitreal injections of VEGF inhibitors or corticosteroids. In advanced cases, vitrectomy may be required.

Despite significant progress in diagnosis and therapy, DR remains a major public health concern, requiring close collaboration between diabetologists, ophthalmologists, and patients. This review summarizes the current understanding of the pathogenesis, classification, diagnostic methods, and

treatment strategies for diabetic retinopathy, with particular emphasis on recent research directions and potential innovative therapeutic approaches.

Keywords diabetic retinopathy, retinal imaging, microvascular complications, OCTA

Introduction

Diabetic retinopathy (DR) is one of the most serious chronic complications of diabetes mellitus (DM) and remains a leading cause of vision loss among working-age adults. The diagnosis of DR is based on characteristic vascular abnormalities in the retina observed during ophthalmic examination. Two major stages of the disease are distinguished: non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). NPDR represents the early stage of the disease, characterized by increased vascular permeability and capillary occlusion. Typical retinal changes at this stage include microaneurysms, small hemorrhages, and hard exudates, which can be detected by fundus photography even though patients may remain asymptomatic. PDR corresponds to the more advanced phase of DR, marked by the development of abnormal new blood vessels. During this stage, significant visual impairment may occur as a result of vitreous hemorrhage or tractional retinal detachment. [1]. The pathophysiology of diabetic retinopathy is driven by prolonged elevations in blood glucose levels that occur in individuals with type 1 or type 2 diabetes despite dietary management, oral antidiabetic medications (such as metformin, sulfonylureas, DPP-4 inhibitors, SGLT2 inhibitors), or insulin therapy. Persistently high glucose levels disrupt multiple biochemical pathways, resulting in excessive production of reactive oxygen species and oxidative stress within retinal tissues. This is accompanied by mitochondrial dysfunction, inflammation, and hypoxia, which together stimulate increased

secretion of VEGF. These processes lead to apoptosis of vascular and neural cells, the formation of abnormal new blood vessels, and heightened vascular permeability. [2] [3]

The clinical significance of DR extends across all demographics, affecting children and the elderly alike. With over 103 million cases reported in 2020, the global prevalence is expected to climb to 161 million by 2045. While early detection is vital for preserving vision, traditional diagnostic tools like OCT and fluorescein angiography often necessitate in-person hospital visits, creating barriers for low-income families and those in remote locations. To address these gaps, recent efforts have shifted toward molecular biomarkers, genetic risk profiling, and AI-driven screening technologies.

Current management relies heavily on laser surgery and intravitreal anti-VEGF injections. Although these treatments help manage vascular leakage, they are not universally successful; for instance, significant visual gains are observed in only 29% of patients with macular edema after two years. Furthermore, the high cost and frequency of these procedures impose a heavy burden on healthcare systems and patients. A particularly daunting challenge is the "metabolic memory" effect, where retinal degeneration continues to advance despite intensive glucose management. This underscores the urgent need for innovative therapeutic strategies that go beyond traditional glycemic control [4].

Pathology in DR

For a significant period, diabetic retinopathy (DR) has been identified primarily as a microvascular disorder. It is widely accepted that elevated blood glucose levels serve as a fundamental driver in the development of retinal capillary damage. This glucose-induced vascular injury is mediated by the activation of several complex metabolic pathways, most notably the polyol pathway, the buildup of advanced glycation end products (AGEs), and the hexosamine and protein kinase C (PKC) signaling cascades [1] [5]. The clinical impact of these metabolic disruptions is widespread, affecting nearly all individuals with type 1 diabetes and approximately two-thirds of those with type 2 diabetes over time. While patients often remain asymptomatic during the initial phases, the progression of the disease typically leads to visual impairment caused by retinal hemorrhages and edema. Clinically, the disease is categorized into non-proliferative (NPDR) and proliferative diabetic retinopathy (PDR). NPDR represents the early stage, characterized by increased vascular permeability and capillary blockage. This stage is graded from mild to severe: mild cases present solely with microaneurysms, whereas severe NPDR is defined by extensive intraretinal hemorrhages across all quadrants, venous beading, or significant microvascular abnormalities, even in the absence of PDR signs.

As retinal hypoxia becomes chronic, the disease may transition into PDR, which is marked by pathological neovascularization. These fragile new vessels are prone to leaking, leading to vitreous hemorrhages and the formation of fibrovascular membranes. Such complications significantly increase the risk of tractional retinal detachment and permanent vision loss. Recent molecular studies have further highlighted the complexity of PDR, identifying elevated levels of proteins like SPARC and inflammatory markers such as IL-8 in the vitreous of affected patients. Furthermore, mRNA sequencing of fibrovascular tissues has revealed an upregulation of genes related to fibrosis, inflammation, and wound healing, which may explain why traditional anti-angiogenic treatments often provide only temporary relief. Without targeted intervention, the advanced structural changes in PDR pose a definitive threat to long-term visual acuity [6].

Risk factors

As the worldwide prevalence of diabetes continues to escalate, identifying the risk factors for diabetic retinopathy (DR) is essential for developing effective prevention and early intervention strategies. These factors are generally categorized into modifiable and non-modifiable variables. Historically, the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) identified several key predictors for the incidence of proliferative DR (PDR) in type 1 diabetic patients, including HbA1c levels, gross proteinuria, body mass index (BMI), and hypertension status. Interestingly, while higher BMI and HbA1c were strongly linked to the progression of existing DR, factors such as smoking status and gender did not show a consistent association with disease incidence in this cohort [Klein et al., 1984].

The impact of hypertension on DR progression has been a subject of clinical debate. Although the WESDR found no direct link between blood pressure levels and disease advancement, the United Kingdom Prospective Diabetes Study (UKPDS) provided contradictory evidence, demonstrating that aggressive management of hypertension could reduce DR progression by as much as 34% [King et al., 1999].

More recent large-scale analyses, such as the study of over 99,000 patients in the Kaiser Permanente system, reinforce the primary role of glycemic control. Patients with poorly managed diabetes (HbA1c $\geq 10.0\%$) face a substantially higher risk of advancing to late-stage DR compared to those maintaining levels below 7.0%. Beyond glucose and blood pressure, cholesterol levels and ethnicity also play significant roles. For instance, non-white populations have been found to experience higher rates of disease progression, whereas Asian patients appear to have a lower predisposition to developing

diabetic macular edema (DME) [Tarasewicz et al., 2023]. These disparities underscore the need for personalized screening protocols that account for both metabolic control and demographic risk profiles [7].

Genetic factors

While the landmark DCCT and UKPDS trials unequivocally established that intensive glycemic management reduces the risk of DR, evidence suggests that 'tight' control alone cannot entirely eliminate microvascular complications. Statistical analyses from the DCCT cohort indicate that cumulative glycemic exposure, measured via HbA1c levels over time, accounts for only approximately 11% of the variation in complication risk. This disparity has led researchers to investigate the hereditary nature of the disease. Notably, diabetic first-degree relatives of patients with severe retinopathy face a risk ratio of 3.1 for developing similar complications compared to those without a family history of severe progression.

Efforts to pinpoint specific genetic markers have proven challenging. Early studies suggested associations between certain human leukocyte antigens (HLA) and PDR, though these effects appeared to be mitigated by high degrees of myopia, which paradoxically offers a protective effect against retinopathy. Large-scale genomic investigations, such as the FIND study—which examined Caucasian, African-American, Hispanic, and Native American cohorts—have sought to identify a definitive genetic basis for DR and diabetic nephropathy, yet no universal 'retinopathy gene' has been confirmed. Despite some suggestive results regarding modifications in the VEGF gene among PDR patients, these findings remain inconsistent across different populations [8]. Ultimately, while the genetic influence on DR pathogenesis is undeniable, the polygenic nature of the disease continues to present a significant hurdle for contemporary genomic research [9].

Diagnosis

A thorough ophthalmic assessment for patients suspected of having diabetic retinopathy (DR) begins with measuring visual acuity and intraocular pressure. This is followed by a slit-lamp biomicroscopy of the anterior segment and, if necessary—particularly in cases of neovascularization of the iris or suspected glaucoma—gonioscopy. However, the cornerstone of DR diagnosis remains a dilated

funduscopy examination, which can be initially performed by general practitioners using direct ophthalmoscopy.

The clinical identification of DR stages relies on specific retinal manifestations. In the non-proliferative stage (NPDR), clinicians primarily look for microaneurysms resulting from pericyte depletion, alongside hard exudates and dot-blot hemorrhages. Other critical indicators of NPDR progression include cotton wool spots—white, ischemic lesions caused by arteriolar obstruction—as well as venous beading and intraretinal microvascular abnormalities (IRMA), which represent remodeled capillary networks in response to widespread occlusion. Conversely, the hallmark of proliferative DR (PDR) is the development of neovascularization, either on the optic disc or in other retinal regions. In its most advanced forms, the growth of fibrous tissue can lead to tractional retinal detachment (TRD), causing significant macular distortion and permanent vision loss [10] [11].

Modern diagnostic approaches have increasingly integrated Artificial Intelligence (AI) to automate the detection and segmentation of DR-related lesions. Deep Learning models, particularly Deep Convolutional Neural Networks (DCNNs), are now employed to identify clinical markers such as microaneurysms, hard exudates, and various types of hemorrhages directly from digital fundus photography. These networks utilize advanced preprocessing techniques—including illumination correction and contrast enhancement (e.g., CLAHE)—to normalize image quality and improve diagnostic accuracy.

Recent research has demonstrated the potential of state-of-the-art architectures, such as Inception V3, ResNet, and VGG16, in localizing pathological features with high precision. For instance, some models have achieved overall accuracies as high as 98.0% in identifying DR lesions within specific image patches. While these AI tools show varying levels of sensitivity for different lesion types—performing particularly well in detecting hemorrhages and cotton wool spots—their ability to process large datasets on standard hardware, such as personal computers or smartphones, marks a significant shift toward accessible, large-scale screening. Furthermore, visualization layers in these networks allow clinicians to see 'prognostic regions,' providing a mechanistic interpretation that aligns with traditional retinal landmarks like the optic disc and fovea [12].

Treatment

The management of diabetic retinopathy (DR) has traditionally centered on a multi-faceted approach involving laser photocoagulation, vitreoretinal surgery, and intensive pharmacological control of systemic risk factors, such as hyperglycemia, hypertension, and hyperlipidemia. These conventional interventions have been instrumental in clinical practice, demonstrating significant success in suppressing retinal neovascularization, reducing macular edema, and addressing the mechanical complications of fibrous tissue proliferation.

While large-scale clinical trials have validated the efficacy of these established treatments, they are not without substantial limitations. The shift from purely surgical and laser-based interventions toward modern pharmacological therapies highlights a growing recognition that while traditional methods are effective at managing the advanced complications of DR, they often address the symptoms rather than the underlying molecular drivers. Consequently, understanding the balance between the proven benefits of traditional therapy and its inherent clinical constraints is essential for optimizing patient outcomes [13].

Laser therapy has been a cornerstone of diabetic retinopathy management since the late 1960s, beginning with ruby laser photocoagulation and later evolving into the more conventional argon laser techniques. The clinical application of these treatments was standardized through two landmark trials: the Diabetic Retinopathy Study (DRS) and the Early Treatment Diabetic Retinopathy Study (ETDRS). These investigations established that panretinal photocoagulation (PRP) significantly reduces the risk of severe vision loss by approximately 60% over two years, particularly in patients exhibiting high-risk proliferative characteristics such as neovascularization of the disc or retina associated with vitreous hemorrhage.

Panretinal photocoagulation operates through several hypothesized mechanisms, although its exact physiological impact is still being studied. It is believed that PRP improves the transport of oxygen and nutrients from the choroid to the retina while facilitating the removal of metabolic waste. By destroying peripheral photoreceptors, the laser reduces the overall metabolic demand of the retina, which in turn leads to a net decrease in the expression of pro-angiogenic cytokines like VEGF. Despite its efficacy in stabilizing vision, PRP is associated with notable side effects, including constricted visual fields and reduced sensitivity to color and contrast.

Beyond managing proliferative stages, focal and grid laser therapies have proven highly effective for treating clinically significant macular edema. Research indicates that focal laser application can halve the incidence of moderate vision loss by directly targeting leaking microaneurysms and stimulating the retinal pigment epithelium (RPE). Furthermore, studies by the DRCR Retina Network have shown that focal-grid treatments often provide more stable long-term results with fewer side effects than certain intravitreal steroid doses. The therapeutic effect likely results from a combination of direct vessel closure, increased oxygenation leading to arteriolar constriction, and a beneficial shift in the biochemical environment of the RPE [14].

However, while laser therapy remained the primary intervention for decades, the emergence of pharmacological treatments has introduced a new era in ocular care. The introduction of anti-vascular endothelial growth factor (anti-VEGF) agents has fundamentally transformed the therapeutic landscape for PDR and DME. This shift has prompted extensive clinical research aimed at comparing the efficacy of standalone pharmacological therapy against traditional retinal photocoagulation, as well as evaluating the potential benefits of combining these two approaches. Central to these efforts has been the DRCR Retina Network (DRCR.net), which has coordinated a series of landmark protocols to determine the optimal treatment paradigms.

In addition to anti-VEGF agents, research has also focused on the utility of intravitreal corticosteroid therapy. Studies have investigated whether steroids, either as a monotherapy or in conjunction with laser treatment, offer superior outcomes for patients with DME compared to conventional photocoagulation alone. These comparative analyses are critical, as they provide the evidence base for modern clinical guidelines, moving away from a 'one-size-fits-all' laser approach toward more personalized, drug-based management strategies [15].

When non-surgical interventions, such as panretinal photocoagulation (PRP) and intravitreal anti-VEGF injections, prove insufficient to manage the advanced complications of proliferative diabetic retinopathy (PDR), Pars Plana Vitrectomy (PPV) remains the definitive surgical solution. While the core principles of PPV have been established for decades, recent technological leaps in microincision instrumentation, advanced imaging systems, and preoperative adjuncts have significantly enhanced the versatility and safety of this procedure.

Modern vitrectomy is no longer seen merely as a last-resort treatment for non-clearing vitreous hemorrhages. Instead, the refinement of surgical techniques and instruments has expanded its

indications to include a wider spectrum of complex cases, such as tractional retinal detachment and fibrovascular proliferation. These advancements allow for more precise tissue manipulation and faster recovery times. However, as the field continues to evolve, clinical experience must be balanced with ongoing empirical research to further delineate the role of vitrectomy in the early management of high-risk diabetic patients [16].

Table 1. Summary of Therapeutic Strategies for Diabetic Retinopathy (DR)

Treatment Modality	Indications	Mechanism of Action	Clinical Benefits	Potential Limitations
Intensive Glycemic & Systemic Control	All stages of DR; Prevention	Reduction of metabolic stress; Stabilization of the blood-retinal barrier.	Reduces incidence and slows progression (DCCT/UKPDS studies).	"Metabolic memory" effect; Difficult long-term patient compliance.
Panretinal Photocoagulation (PRP)	High-risk PDR; Severe NPDR	Destruction of hypoxic peripheral retina to reduce VEGF production.	60% reduction in severe vision loss; Long-term stability.	Permanent loss of peripheral field; Reduced night vision and contrast.
Focal/Grid Laser Therapy	Clinically Significant Macular Edema (CSME)	Direct closure of microaneurysms; Stimulation of the RPE.	Effective for non-center-involved edema; Historically stable results.	Risk of subretinal fibrosis; Less effective than anti-VEGF for central edema.
Anti-VEGF Therapy	PDR and Center-Involved DME	Blocking vascular endothelial growth factor (VEGF) signaling.	Rapid improvement in visual acuity; Minimally invasive (injections).	Requires frequent injections; High socioeconomic burden and costs.
Intravitreal Corticosteroids	Refractory DME	Inhibition of inflammatory pathways and cytokine release.	Reduces macular thickness in chronic, resistant cases.	Risk of cataract formation and increased intraocular pressure (glaucoma).
Pars Plana Vitrectomy (PPV)	Vitreous hemorrhage; Tractional retinal detachment	Mechanical removal of vitreous gel and fibrovascular membranes.	Restores vision in advanced PDR; Repairs structural damage.	Invasive surgical procedure; Requires specialized surgical expertise.

Modern Perspectives on DR: Molecular Biomarkers and Early Prediction

A critical challenge in managing diabetic retinopathy is its progressive nature, often remaining clinically silent until advanced stages. Therefore, the identification of early biomarkers is essential for predicting disease progression and implementing preventive strategies before irreversible damage occurs. Recent research has shifted focus toward subclinical inflammatory markers that precede visible retinal lesions. For instance, **Mysona et al.** identified that an imbalance in the proNGF/NGF ratio in the serum mirrors changes found in the vitreous of PDR patients, suggesting that a simple blood test could serve as a novel systemic biomarker for retinal health.

Furthermore, the role of inflammation as a primary driver of DR has led to the investigation of cytokines within the ocular environment. While vitreous sampling is invasive, studies by **Dong et al.** have demonstrated that concentrations of inflammatory cytokines—such as IL-1 β , IL-6, MCP-1, and VEGF—in the aqueous humor are positively correlated with the severity of macular edema. Conversely, levels of anti-inflammatory cytokines like IL-10 and IL-12 show a negative association, providing a biochemical profile of retinal stress. Emerging research even explores the use of tears as a non-invasive source of these biomarkers. By identifying these molecular signals early, healthcare providers can better stratify patient risk and initiate intensive metabolic or pharmacological interventions at the most opportune moment [17].

Metabolic memory

A significant challenge in managing diabetic retinopathy is its persistence despite stabilized blood glucose levels, a phenomenon known as 'metabolic memory' (MM). This clinical state is driven by complex biochemical, structural, and genomic alterations at the cellular level, which can make DR progression refractory to even long-sustained glycemic improvements. The concept of MM originated from longitudinal clinical observations, where patients who received early, intensive treatment for hyperglycemia experienced long-term protective effects on their retinal health, regardless of their glycemic status in later years. Conversely, those with poor initial control faced a continued worsening of vascular and neurodegenerative changes even after achieving 'reasonable' systemic stabilization.

Preclinical and clinical studies emphasize that the period between the onset of diabetes and the development of vision-threatening DR (VTDR) represents a critical 'therapeutic window.' During this

time lag, the cellular environment undergoes epigenetic modifications and experiences chronic oxidative stress that can perpetuate inflammatory pathways. Understanding MM is vital because it highlights that early intervention is not merely beneficial but essential to prevent the retina from entering a self-sustaining state of decline. Consequently, targeting the molecular drivers of metabolic memory offers a promising new frontier for therapeutics designed to retard the progression from nonproliferative to advanced stages of the disease [18] [19] [20].

Conclusion

The comprehensive analysis of diabetic retinopathy (DR) presented in this work leads to the following key conclusions regarding its pathogenesis, diagnosis, and management:

1. **Multifactorial Pathogenesis and the "Metabolic Memory":** While hyperglycemia is the primary initiator of retinal damage, the progression of DR is driven by a complex interplay of biochemical pathways, including oxidative stress, inflammatory cytokine release (notably VEGF), and epigenetic modifications. The phenomenon of metabolic memory underscores the critical importance of early intensive glycemic control, as early cellular insults can perpetuate vascular damage even after systemic stabilization is achieved.
2. **Revolution in Diagnostics through AI and Advanced Imaging:** The integration of Optical Coherence Tomography (OCT/OCTA) and Artificial Intelligence (AI) has fundamentally transformed DR screening. These technologies allow for the detection of subclinical changes, such as foveal avascular zone alterations and early macular edema, which are often invisible during traditional ophthalmoscopy. Automated AI-based screening offers a scalable solution to the global burden of diabetes, particularly in underserved regions.
3. **Evolution of Therapeutic Paradigms:** The management of vision-threatening DR has shifted from purely destructive laser techniques to personalized pharmacological interventions. While panretinal photocoagulation (PRP) remains essential for stabilizing advanced stages, intravitreal anti-VEGF therapy has become the gold standard for improving visual acuity in patients with macular edema. In refractory cases, modern microincision vitrectomy (PPV) offers a high success rate in restoring vision and preventing tractional retinal detachment.
4. **The Essential Role of Lifestyle and Biomarkers:** Future strategies in DR management must prioritize secondary prevention. The identification of novel biomarkers in serum, aqueous humor, or tears provides a promising pathway for individualized risk stratification. Ultimately, however, pharmacological success must be supported by systemic patient management,

including physical activity and dietary modifications, which remain the most cost-effective pillars of public health.

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Author's contribution

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