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REVIEW ARTICLE

Diabetic retinopathy: pathogenesis, pathophysiology, and treatment

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ABSTRACT

Diabetic retinopathy (DR) is the most common microvascular complication of diabetes mellitus (DM) and one of the leading causes of vision impairment worldwide. Prolonged hyperglycemia initiates a cascade of molecular events including chronic inflammation, oxidative stress, advanced glycation end products, and the activation of plasma kallikrein and protein kinase C signaling pathways, which leads to endothelial damage and pericyte loss. The resulting endothelial barrier dysfunction promotes serum leakage and retinal edema, while advanced disease stages are characterized by ischemia-driven retinal neovascularization mediated by elevated intraocular vascular endothelial growth factor (VEGF) levels. Current therapeutic strategies for diabetic retinopathy include laser therapy, intravitreal administration of anti-VEGF agents or corticosteroids, and vitreoretinal surgery. Despite their efficacy, a number of patients experience suboptimal responses. Consequently, novel therapeutic approaches are under investigation, including alternative anti-angiogenic agents, gene therapies, and visual cycle modulators currently undergoing clinical trials. A comprehensive understanding of the pathogenesis and pathophysiology of diabetic retinopathy is essential to improve existing treatment modalities and address current limitations in patient outcomes. In this review, we systematically searched and analyzed articles published in English from 2014 to 2024 using PubMed, ScienceDirect, SpringerLink, and Google Scholar. Relevant search terms included “diabetic retinopathy,” “pathophysiology,” “pathogenesis,” “treatment,” and “diabetic macular edema.” This review presents recent insights into the pathogenesis of diabetic retinopathy, including oxidative stress, inflammation, and neurodegeneration, followed by an overview of its pathophysiology such as microvascular dysfunction and neovascularization. Finally, current and emerging treatment modalities, encompassing both pharmacological and surgical approaches, are discussed. This structured approach provides essential background to understand the complexity of diabetic retinopathy and recent advances in its management.

Keywords: Diabetic retinopathy; pathogenesis; pathophysiology; medical treatment; surgical treatment

INTRODUCTION

Diabetes mellitus (DM) is the most prevalent metabolic disorder worldwide, with an increasing prevalence, especially in young adults, leading to a greater burden from its complications.[1] Diabetic retinopathy (DR), a major complication of DM, is a leading cause of blindness globally.[2] The International Diabetes Federation estimated that in 2019, around 463 million people in the world suffered from diabetes and this number is projected to rise to 700 million by the year 2045.[3] Among individuals with diabetes, the global prevalence is 22.27% for DR, 4.07% for clinically significant macular edema, and 6.17% for vision-threatening DR.[2]

In 2010, the prevalence of DM in Indonesia was around 6.9 million young adults, and this number is expected to rise to 12 million by 2030 with retinopathy complications of around 43.1%. In Indonesia, type 2 diabetes is predicted to affect 6.9% of the population in 2025, or around 20 million individuals, with an estimated 8.5 million suffering from retinopathy.[1] Based on the 2023 Indonesian Health Survey by the Ministry of Health of the Republic of Indonesia, prevalence of diabetes mellitus reached 11.7% and contributed 10.5% to the cause of disability in society.[4]

Diabetic microvascular disease arises from prolonged hyperglycemia, disrupting key biochemical and molecular pathways, such as oxidative stress, advanced glycation end products (AGEs), and activation of plasma kallikrein and protein kinase C (PKC), leading to endothelial damage and pericyte loss. Neurological changes, such as thinning of inner retinal layers, functional impairment, and neural disorganization can precede visible vascular damage. As the disease advances, retinal capillary changes, including basement membrane thickening and pericyte dropout, cause occlusion and nonperfusion.[5]

High-resolution imaging, including adaptive optics and optical coherence tomography angiography, reveals early vascular remodeling that worsens over time. Endothelial barrier breakdown causes fluid leakage and edema, while vascular endothelial growth factor (VEGF) elevation from ischemic retina drives neovascularization. Despite these insights, the mechanisms of DR progression remain unclear.[5] This review provides an updated overview of the pathogenesis, pathophysiology, and treatment of DR, synthesizing recent findings on disease mechanisms and current as well as emerging therapeutic strategies to address ongoing clinical challenges.

METHODS

In this review, we searched the literature for articles on diabetic retinopathy published in English or Indonesian between 2014 and 2024. Relevant articles were retrieved from PubMed, ScienceDirect, SpringerLink, and Google Scholar using the keywords: "diabetic retinopathy," "pathophysiology," "pathogenesis," "treatment," and "diabetic macular edema". The search initially yielded 4,033 articles. After removing duplicates, inaccessible full texts, and articles not relevant to the review objectives, 3,973 articles were excluded. A total of 58 articles were selected for analysis and synthesis (as shown in Figure 1). The selected articles were reviewed to identify key findings related to the pathogenesis, pathophysiology, and treatment of diabetic retinopathy. Their content was thematically grouped and narratively synthesized to provide a comprehensive overview of current understanding and management strategies.

PATHOGENESIS

Aldose reductase (Polyol pathway)

Under hyperglycemic conditions, multiple pathways are activated to manage elevated glucose levels, leading to an increase in reactive oxygen species (ROS).[6] Aldose reductase (AR) and sorbitol dehydrogenase (SDH) catalyze the polyol pathway, converting glucose into sorbitol with nicotinamide adenine dinucleotide (NAD)-phosphate as a cofactor, and subsequently transforming sorbitol into fructose, resulting in the production of nicotinamide adenine dinucleotide hydrogen (NADH).[7] This process contributes to diabetic complications such as neuropathy, nephropathy, and retinopathy, as a result of sorbitol accumulation, excessive NADH production, and NADPH depletion.[7] Aldose reductase plays a significant role in diabetes-related retinal damage by activating glial fibrillary acidic protein, particularly in Müller cells, which regulate vascular permeability and cell survival.[7] Damage to Müller cells impairs neurovascular coupling in the retina, resulting in glutamate accumulation and altered mitochondrial NAD+/NADH ratios.[7,8] Additionally, fructose

from SDH reactions contributes to advanced glycation end-products (AGEs), which interact with receptors, triggering signaling pathways that exacerbate DR.[6–9]

The activity of AR in DR is associated with oxidative stress, inflammatory responses, and disruptions in arachidonic acid metabolism.[7] Overactive AR leads to the production of protein kinase C, the activation of oxidative and nitrosative stress pathways, and the upregulation of cyclooxygenase-2 and transcription factors such as activator protein-1 and nuclear factor-kappa B (NF-κB).[6,9] Aldose reductase also increases the ratio of activated to total JNK1/2 and ERK1/2, driving processes such as apoptosis and cell proliferation.[7] Furthermore, the non-enzymatic glycation facilitated by fructose generates fructose-3-phosphate and AGEs, intensifying oxidative damage and contributing to the progression of DR.[6] The interaction of these mechanisms underscores the significant role of aldose reductase in the development of diabetic complications, especially in the retina.[7,9]

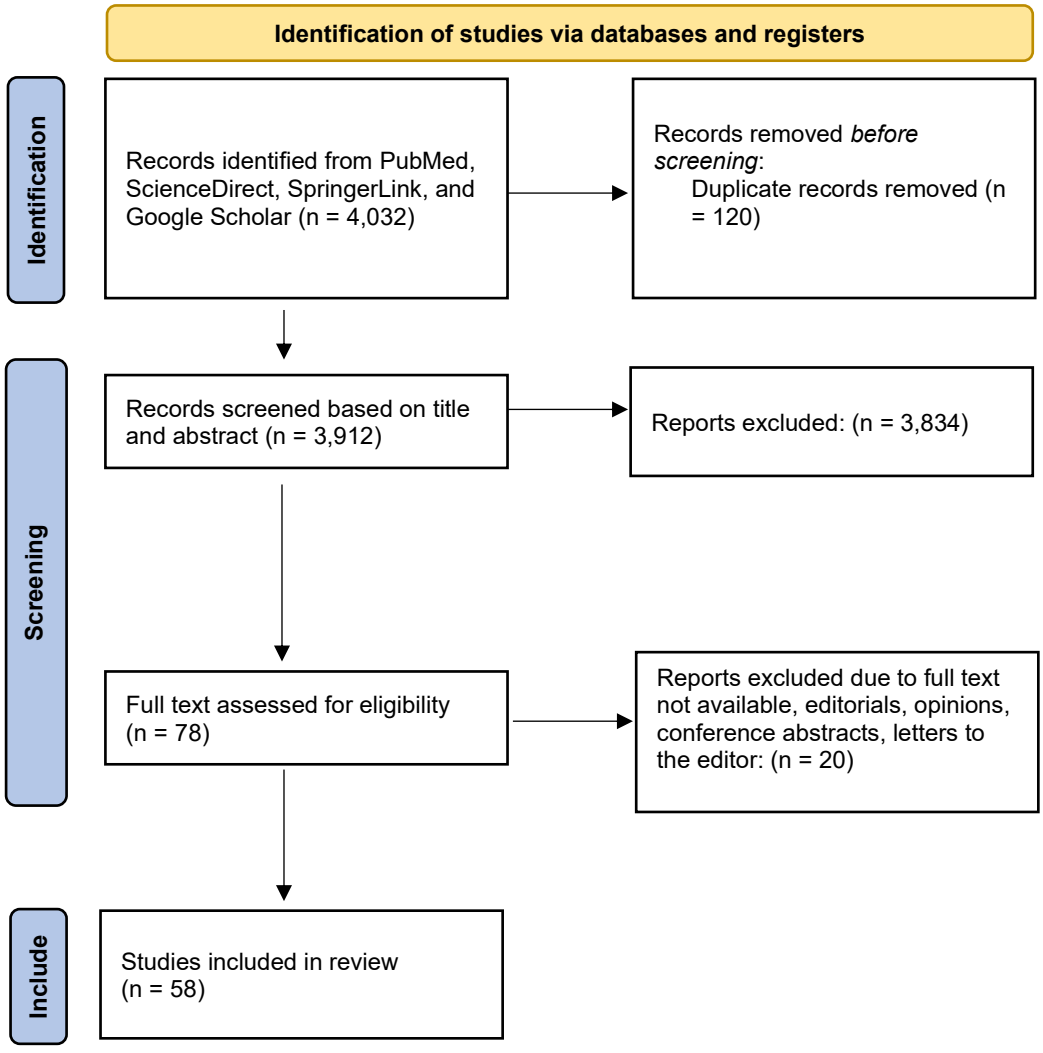

Figure 1. Schematic process of study selection

Advanced glycation end products

Advanced glycation end products (AGEs) are proteins or lipids that undergo glycation as a result of exposure to sugars, with dietary intake being the primary source.[6,10] When the body's capacity to eliminate AGEs is exceeded, these AGEs begin to accumulate. Research has shown that numerous chronic disorders are associated with elevated levels of AGEs, particularly diabetes. Persistent hyperglycemia significantly enhances the nonenzymatic glycosylation of macromolecules such as proteins and lipids, ultimately resulting in AGE buildup. In diabetic patients, AGEs have been identified in retinal blood vessels, with their

presence correlating to the severity of retinopathy, underscoring their role in the progression of DR.[6] Advanced glycation end products were also discovered to accumulate in the endothelial cells of the retina, leading to capillary occlusion. This process occurs through elevated levels of intracellular cell adhesion molecules, ultimately resulting in retinal ischemia.[8,10]

The detrimental effects of AGEs often occur through their interaction with the receptor for AGEs (RAGE) on cell surfaces.[6,11] This interaction triggers the activation of NF-κB, which contributes to pericyte apoptosis in the retina and promotes the expression of VEGF, increasing vascular endothelial permeability. Furthermore, AGEs significantly contribute to the production of reactive oxygen species (ROS), which is essential in the pathophysiology of DR. Through their interaction with RAGE, AGEs activate NADPH oxidases, thereby amplifying intracellular ROS generation and further exacerbating retinal damage.[6,12]

Photoreceptor metabolism

Photoreceptor cells are specialized neurons in the retina responsible for transforming light into neural signals which are relayed to the brain for image interpretation. Photoreceptors can be classified as either rods or cones. In contrast to rods, which have poor spatial resolution and great light sensitivity, cones have high spatial resolution and low light sensitivity.[13] As the first neurons in the visual circuit, photoreceptors play a significant role in retinal vascular diseases, including DR. The retina's unique metabolic demands, driven by photoreceptors as the most energy-intensive cells, make it highly susceptible to damage from diabetes-induced metabolic disruptions. Additionally, the level of illumination affects photoreceptor energy consumption, suggesting that light exposure may influence the onset and progression of retinal diseases such as DR.[14]

Rod cells, in particular, require four times more energy in darkness than in light. Research suggests that dark-adapted rod cells, which demand high oxygen levels, may contribute to retinal degenerative conditions such as DR by reducing PO_2 in the inner retina. Under hyperglycemic conditions, this pseudohypoxia, coupled with anoxia during dark adaptation, promotes VEGF production, exacerbating vascular complications. The effectiveness of panretinal photocoagulation in reducing retinal PO_2 supports this hypothesis. Additional research is required to provide insight into the role of hypoxia in DR progression and to evaluate whether interventions such as oxygen therapy or light adaptation could mitigate disease advancement.[15]

Oxidative stress

Oxidative stress is a significant factor in the progression of DR. In hyperglycemic conditions, excessive ROS are produced in the retina, leading to mitochondrial dysfunction. The overaccumulation of ROS damages tissues surrounding retinal blood vessels, contributing to the progression of DR.[15] Four primary metabolic pathways are implicated in hyperglycemia-induced oxidative damage: activation of the PKC pathway, enhanced flux through the polyol pathway, activation of the hexosamine pathway, and formation of AGEs.[6]

In addition to these metabolic disturbances, other mechanisms also play a role in ROS overproduction in DR. [16] These include abnormal epigenetic modifications, dysregulated nuclear factor activity, such as hyperactivation of NF-κB, and reduced activity of nuclear Nrf2 or NFE2L2.[6,17] Furthermore, hyperglycemia-induced mitochondrial dysfunction exacerbates oxidative stress, highlighting the multifaceted nature of ROS involvement in DR pathogenesis.[6,16,17]

Protein kinase C activation

The protein kinase C (PKC) pathway is pivotal in the development of DR triggered by oxidative stress. The PKC family comprises several isoforms, notably PKC-α, -β, -δ, and -ε, which become activated during DR progression. Elevated blood sugar levels increase glucose flux through glycolysis, leading to enhanced diacylglycerol synthesis, a key PKC activator within cells. In retinal cells, PKC regulates various physiological processes, including retinal blood flow, endothelial permeability, leukocyte activation and adhesion (leukostasis), and VEGF expression. Additionally, PKC can boost NADPH oxidase activity, promoting ROS production in diverse vascular cells including endothelial cells, smooth muscle cells, pericytes, and mesangial cells. Consequently, hyperglycemia-induced PKC activation exacerbates oxidative stress in retinal cells, contributing to DR pathogenesis.[18,19]

PATHOPHYSIOLOGY

Retinal microvasculopathy

Diabetic retinopathy has been widely acknowledged as a microvascular condition. Elevated blood glucose levels are considered to significantly contribute to the development of retinal microvascular injury. Various metabolic pathways contribute to hyperglycemia-induced vascular damage, including the polyol pathway, the accumulation of AGEs, the PKC pathway, and the hexosamine pathway.[19] The reduced number of endothelial cells and pericytes leads to capillary obstruction and ischemia. Retinal ischemia promotes hypoxia-inducible factor 1 (HIF-1) leading to an elevation in VEGF levels.[20,21] Additional data indicates that elevated phospholipase A2 (PLA2) in diabetes also causes VEGF to be upregulated. VEGF plays a crucial role in the advancement of proliferative diabetic retinopathy (PDR) and diabetic macular edema (DME) by increasing vascular permeability via the phosphorylation of tight junction proteins, including occludin and zonula occludens-1.[19] Additionally, VEGF activates mitogen-activated protein kinase (MAPK) to stimulate endothelial cell proliferation as an angiogenic agent. Elevated expression of VEGF has been observed in the vitreous of individuals with DME and PDR, as well as in the retina of diabetic mice.[19–21]

Interactions with the endothelial receptor tyrosine kinase Tie2 suggest that other angiogenic factors, including angiopoietin (Ang-1, Ang-2), contribute to the regulation of vascular permeability. It has been demonstrated that the Tie2 antagonist Ang-2 causes more vascular leakage in the retina of diabetic mice. Other angiogenic factors than VEGF have been proposed as potential contributors to microvascular alterations during DR; hence, they might offer novel targets for treatment.[19]

Retinal inflammation

Inflammation is a crucial component in the pathogenesis of DR. Chronic low-grade inflammation has been extensively acknowledged at various stages of diabetes mellitus in both humans and animal models.[22] An important mechanism in the initial phases of DR has been identified as leukostasis.[19] Subsequent research revealed that leukostasis activates the Fas (CD95)/Fas-ligand pathway, which in turn leads to endothelial cell death and blood retinal barrier breakdown.[19] Leukostasis in diabetes has been linked to leukocyte-endothelial adhesion mediated by adhesion molecules.[19,23–25]

There have been reports of elevated chemokines in diabetes individuals, including macrophage inflammatory protein-1 alpha and beta (MIP-1α and MIP-1β) and monocyte chemotactic protein-1 (MCP-1). MCP-1 deficiency in diabetic mice results in decreased retinal vascular leakage.[19,23] Diabetic patients exhibited significantly elevated expression levels of inflammatory cytokines, including interleukin 6 (IL-6), IL-8, IL-1β, and tumor necrosis factor alpha (TNF-α), which were associated with the progression of DR.[20,21] Retinal inflammation is also believed to be initiated and amplified by malfunctioning of retinal glial cells. Microglia get activated in response to hyperglycemic stress, leading to an increase in the release of TNF-α, IL-6, MCP-1, and VEGF.[19–21, 23,24]

While inflammatory factors might offer protective effects during the initial stages of DR, prolonged inflammation can lead to cytotoxic damage. For instance, inflammation-induced impairment of pericytes, which are crucial for maintaining the vascular barrier, results in the breakdown of the BRB, thereby accelerating DR progression. IL-1β, a key inflammatory mediator synthesized by endothelial cells and microglia, is crucial in this process. Activation of IL-1β by NF-κB induces pericyte apoptosis and diminishes tight junction proteins in endothelial cells, leading to increased endothelial permeability.[23]

Retinal neurodegeneration

Clinical classifications of DR focus on neovascularization, but research shows that neuronal and glial changes often precede vascular proliferation. Neurodegeneration in DR is linked to oxidative stress, impaired antioxidant defenses, neuroprotective factor imbalances, glutamate excitotoxicity, mitochondrial dysfunction, renin-angiotensin system activation, and tau protein phosphorylation. Reduced levels of neuroprotective factors such include interstitial retinol-binding protein (IRBP), somatostatin, and pigment epithelium-derived growth factor (PEDF) are consistently observed, with IRBP decrease occurring in early stage and closely tied to neurodegeneration. While neuroprotective factors decline, molecules such as VEGF and erythropoietin increase, highlighting a complex interaction between neurodegenerative and survival pathways. Evidence suggests neurodegeneration may drive vascular

degeneration, indicating neuronal damage may play a more significant role in early DR than vascular changes. Long-term studies show retinal neurodegeneration, marked by nerve fiber and ganglion cell layer thinning, can develop without visible vascular damage. Early functional impairments include reduced electrical responses and contrast sensitivity.[25] In diabetic mice, retinal neuron apoptosis occurs within a month of diabetes. In diabetic retinas, pro-apoptotic molecules such caspase-3, Bax, and Fas are upregulated. Retinal degeneration is associated with mitochondrial dysfunction, and diabetic donor eyes produce more pro-apoptotic proteins such as cytochrome C and apoptosis-inducing factor. Research conducted in vitro indicates that elevated exposure to glucose is linked to a higher rate of mitochondrial fragmentation and death in cells. Retinal neuron death caused by caspase-3 and visual impairment are both successfully inhibited by suppressing ROS production. There is mounting evidence that the etiology of DR may involve retinal neurodegeneration as a separate entity. Evidence suggests that retinal neurodegeneration may serve as a distinct variable in DR. Prior to microvascular changes, a reduction in ganglion cell and retinal thinning were noted in diabetic mice. Further research into the molecular pathways of neurodegeneration may offer new treatment strategies for early DR intervention.[19]

Angiogenesis and neovascularization

Angiogenesis is a multi-step, intricate process that involves interactions between extracellular matrix components, signaling molecules, and cell surface receptors. Endothelial cells are the primary drivers of this process, which also requires the involvement of other cell types.[26] In DR, hyperglycemia disrupts the equilibrium between angiogenic promoters and inhibitors, fostering the formation of immature, leaky blood vessels that contribute to complications. Hypoxia exacerbates this condition by inducing the release of pro-angiogenic factors which detaches pericytes from vessel walls, weakens endothelial cohesion, and increases vascular permeability.[27] Activated endothelial cells adopt a "pro-angiogenic phenotype," proliferating and migrating along a chemotactic gradient, eventually forming new vessels that mature through basement membrane deposition and pericyte recruitment.[23,27]

Micro-occlusions within the retinal microvasculature are another characteristic feature of DR. Hypoperfusion occurs in areas where retinal arteries and arterioles constrict, which are associated with elevated levels of HIF-1, particularly in PDR. HIF-1 promotes neovascularization by upregulating various growth factors, cytokines, and chemokines, including VEGF, fibroblast growth factor 2 (FGF2), erythropoietin, and interleukins. At the same time, anti-angiogenic mediators such as angiostatin and PEDF are downregulated, with decreased levels observed in the vitreous of diabetic patients. This disparity between pro- and anti-angiogenic factors further drives pathological vessel formation in DR.[23,27]

Chronic inflammation is important to the advancement of DR and is closely associated with neovascularization. Activated retinal microglia release cytokines and pro-angiogenic factors, sustaining ongoing inflammation and vascular damage. This prolonged inflammatory response contributes to macular edema and encourages the formation of new, abnormal blood vessels. Additionally, inflammation may contribute to retinal neurodegeneration, a common feature in DR patients. A deeper understanding of the interplay between inflammation and angiogenesis in DR could pave the way for novel therapeutic strategies, potentially involving a combination of anti-angiogenic and anti-inflammatory treatments to better manage this disease.[26,27] Figure 2 presents a schematic overview of the pathogenesis and pathophysiology of DR.

TREATMENT

Interventions to lower the risk of vision impairment caused by DR can be grouped into three main categories: preventing the onset of microvascular complications, detecting retinopathy at an early stage, and effectively managing the condition once it has developed. Maintaining regulated blood sugar levels and blood pressure is crucial in slowing the progression and severity of DR.[28] Treatment options for diabetic eye disease include intraocular methods, such as laser treatment, intravitreal injections of anti-angiogenic and anti-inflammatory agents, and vitreoretinal surgery. Current therapeutic approaches primarily target advanced stages of the disease, particularly in the presence of PDR or DME.[29]

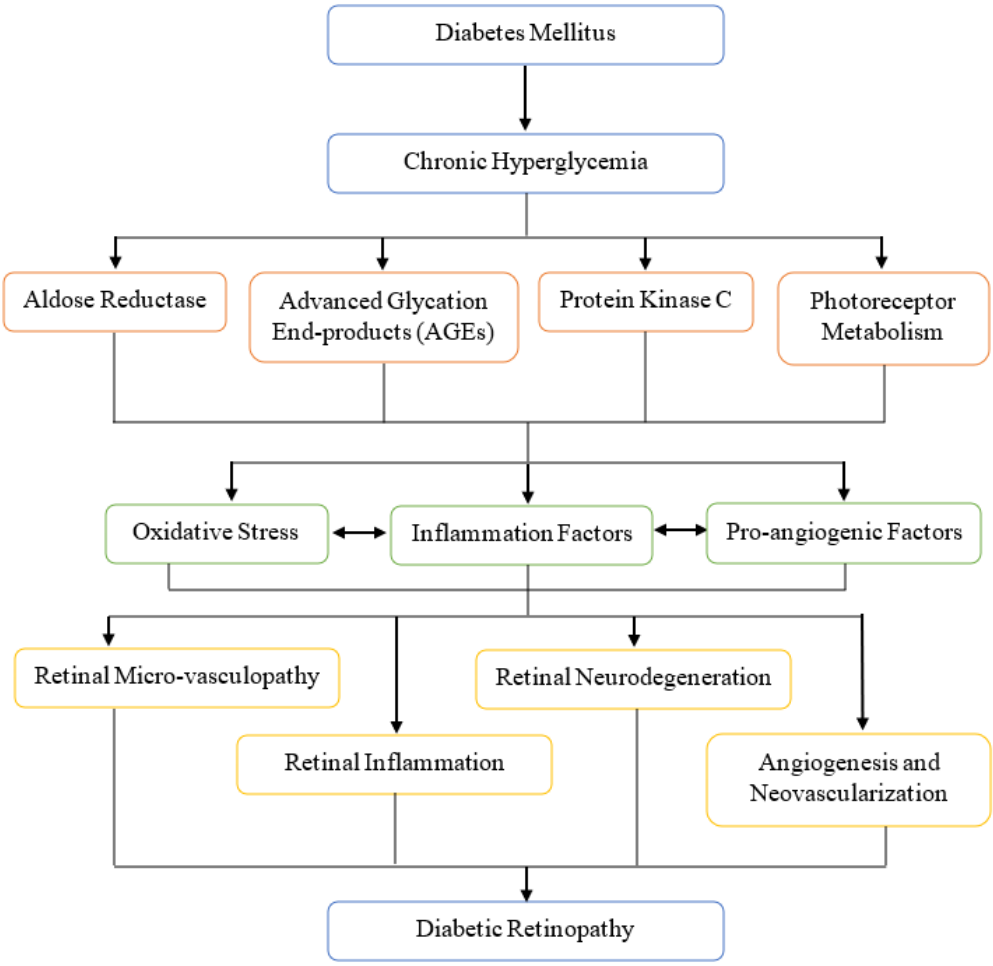

Figure 2. Schematic overview of pathogenesis and pathophysiology of DR

Laser treatment

Pan-retinal photocoagulation (PRP) was introduced as a treatment for PDR in the 1960s. Although initially met with skepticism regarding its ability to induce regression of retinal neovascularization through thermal burns applied to the peripheral retina, its effectiveness was firmly established by the nationwide multicenter Diabetic Retinopathy Study. Additionally, the Early Treatment Diabetic Retinopathy Study later demonstrated that a gentler focal/grid laser technique targeting the central retina could reduce the likelihood of significant vision loss in eyes with DME by 50% over three years.[29]

Subthreshold laser (STL) is an advanced laser technology that applies a grid pattern of non-photocoagulation laser points to "photo stimulate" external retinal layers, particularly the retinal pigment epithelium (RPE). This stimulation promotes the release of metabolites that suppress neovascularization and mitigate vascular permeability.[30] Additionally, STL helps regulate the reduction of mediators responsible for increasing vascular permeability and neovascularization. Unlike continuous wave lasers, STL achieves these therapeutic benefits while minimizing adverse side effects.[31]

Targeted retinal photocoagulation (TRP) focuses on selective photocoagulation of regions affected by retinal vascular occlusion. Studies have indicated that selective photocoagulation can slow the progression of PDR in patients with extensive non-perfused areas measuring one papillary diameter or more.[32] Furthermore, a randomized clinical trial demonstrated that extended TRP effectively promotes early regression of PDR while requiring fewer coagulation spots compared to conventional PRP.[33]

The pattern scanning laser (PASCAL) represents a modern approach to treating DME and PDR. This method minimizes retinal damage

by offering enhanced precision in laser application and reducing treatment duration. Additionally, micro pulse techniques, such as the subthreshold micro pulse diode laser, have been developed to deliver subthreshold burns while minimizing collateral damage to surrounding tissues.[19] Another advancement in retinal laser therapy is the navigated laser (NAVILAS) system, which incorporates a back-of-the-eye camera integrated with retinal eye-tracking technology. This innovation allows ophthalmologists to capture a detailed retinal image of patients with DR or DME, define the treatment areas digitally, and use the system to automatically deliver laser spots to the designated regions.[31,32,34]

The addition of focal laser to anti-VEGF therapy in DME has been shown to reduce injection frequency while maintaining visual outcomes. Its use, particularly with imaging-guided or subthreshold techniques, can further lower treatment burden compared with anti-VEGF monotherapy.[35,36] An overview of retinal laser therapies is shown in Table 1.

Table 1. Laser photocoagulation for the treatment of DR.

Treatment	Mechanism	Clinical benefits
Panretinal photocoagulation	Thermal burns targeting peripheral retina to reduce neovascularization.	Lowers the risk of significant visual impairment in PDR patients.
Subthreshold laser	Stimulates external retinal layers to enhance metabolite production and suppress vascular permeability.	Improves vascular stability while minimizing collateral damage.
Targeted retinal photocoagulation	Selective photocoagulation of occluded retinal regions to slow progression of PDR.	Slows PDR progression; fewer laser spots compared to conventional methods.

Anti-angiogenic treatment

Vascular endothelial growth factor (VEGF) is important to the advancement of DR. Introduction of anti-VEGF therapies has significantly transformed DR management. Anti-VEGF agents evaluated in clinical trials for DR therapy comprise the FDA-approved drugs pegaptanib, ranibizumab, and aflibercept, as well as the off-label use of intravitreal bevacizumab. Modern phase 3 clinical trials have established that intravitreal anti-VEGF injections surpass laser monotherapy in increasing the chances of vision improvement and minimizing vision loss in DME patients. A recent comparison analysis of the three most prevalent anti-VEGF medicines confirmed their effectiveness in improving visual outcomes over one- and two-year treatment periods for DME.[19,29,31]

The RESOLVE [19] and RESTORE [32] studies demonstrated that anti-VEGF therapy with ranibizumab led to significantly greater improvements in visual acuity compared to PRP in patients with PDR. Moreover, the anti-VEGF treatment group exhibited less peripheral visual field loss, a lower incidence of DME, and reduced need for vitrectomy compared to the PRP group. Additional studies have corroborated these findings, showing that intravitreal anti-VEGF therapy, such as ranibizumab, improves Diabetic Retinopathy Severity Scale scores, while also reducing the risks of vitrectomy and DME more effectively than PRP.[19,32]

The VISTA and VIVID trials highlighted that intravitreal aflibercept achieved better visual outcomes compared to standard laser therapy in DME individuals.[37,38] Additionally, the DRCR.net Protocol S [39] and CLARITY [40] studies revealed the efficacy of anti-VEGF medicines in the treatment of PDR. Furthermore, findings from the DRCR.net Protocol T trial revealed that aflibercept outperformed ranibizumab and bevacizumab in enhancing visual acuity, particularly in individuals with moderate to severe baseline visual impairment.[41]

Despite its effectiveness, anti-VEGF therapy presents several limitations and potential adverse effects. The brief half-life of anti-VEGF medicines requires monthly or twice a month treatment to sustain therapeutic effectiveness. Discontinuation of treatment has been associated with poorer outcomes compared to photocoagulation. Frequent intravitreal injections carry a rare but serious risk of endophthalmitis, an inflammatory condition that can significantly affect ocular health.[19,33] Anti-angiogenic agents are summarized in Table 2.

Table 2. Anti-angiogenic agents for the treatment of DR.

Treatment	Mechanism	Clinical benefits
Anti-VEGF Agents (Bevacizumab, Ranibizumab, Aflibercept)	Inhibits VEGF to diminish neovascularization and macular edema.	Improves visual acuity, reduces DME, and lowers risk of vitrectomy.

Anti-inflammatory treatment

The crucial role of inflammation in the etiology of DR made corticosteroids an essential component in its management, particularly for DME.[28] Research on corticosteroid therapy for DR has primarily focused on agents such as triamcinolone acetonide, dexamethasone, and fluocinolone acetonide.[31] These steroids exert anti-inflammatory effects by suppressing both pro-inflammatory and pro-angiogenic mediators, which are key contributors to DME progression.[32]

Chronic inflammation central role in the development of DR results in the discovery of various novel therapeutic targets aimed at regulating cytokine and chemokine release. These targets include the direct or indirect inhibition of interleukins, proteases, chemokines, TNF, angiopoietin-2, and kallikrein. TNF is particularly significant, as it is implicated in both systemic inflammatory conditions and DR. Similarly, angiopoietin-2 is a key mediator that contributes to increased vascular permeability in DR. Corticosteroids, known for their potent anti-inflammatory and antiangiogenic properties, provide a strong basis for their use in managing PDR. However, their application is associated with potential side effects, including cataract formation, glaucoma, and infection.[31,32]

The Diabetic Retinopathy Clinical Research Network (DRCR.net) evaluated intravitreal triamcinolone for DME in studies involving 840 eyes. Two administrations of triamcinolone were evaluated against focal/grid laser photocoagulation. At four months of treatment, the 4 mg triamcinolone group showed enhanced visual acuity (VA), however, at 16 months and beyond, the laser group had superior VA with fewer glaucoma and cataract cases. A subsequent trial compared laser monotherapy to triamcinolone combined with laser and ranibizumab. At 24 weeks, the combination therapy showed better VA, but by one and two years, outcomes were similar, with the triamcinolone group experiencing higher cataract and IOP rates. Pseudophakic patients benefited more from triamcinolone plus laser, comparable to ranibizumab.[31]

Dexamethasone (DEX),[42] delivered via the Ozurdex implant, effectively reduces inflammation and vascular permeability in DME. Clinical trials such as MEAD showed significant VA improvements and macular edema reduction, with effects peaking at two months and lasting up to six months, requiring fewer injections than anti-VEGF agents. However, DEX can raise intraocular pressure (IOP) and accelerate cataract progression, particularly in phakic patients. In the MEAD study, 25% experienced IOP elevation, with some needing surgery, and cataracts developed in 50-60% of phakic eyes over three years. Despite risks, systemic side effects are rare, and its safety profile remains favorable.[42,43]

Fluocinolone acetonide (FA) [43] is a long-acting intravitreal corticosteroid used for particularly in patients who do not respond adequately to other treatments. Administered via the ILUVIEN implant, FA delivers a continuous, low-dose release of the drug for up to 36 months, reducing inflammation and vascular permeability by targeting multiple inflammatory pathways.[43] The FAME study demonstrated its effectiveness in decreasing central retinal thickness and enhancing visual acuity.[32] Over three years, the FA implant showed an average gain of 3.6 to 11 letters in visual acuity and stabilization of anatomical outcomes. These results were more pronounced in chronic cases, emphasizing its effectiveness in eyes that were refractory to other treatments. Side effects included IOP elevation and cataract progression, with 34% requiring medical IOP management and 5% needing surgery. Cataracts developed in up to 82% of phakic eyes, often requiring surgery within 18 months. However, these risks were significantly lower in pseudophakic patients. The sustained-release mechanism of the FA implant reduces the frequency of interventions, offering convenience and improving patient compliance, particularly in populations requiring long-term management. By providing durable visual and anatomical stability, FA represents a vital option for addressing the

complex needs of chronic DME patients, especially those with limited treatment alternatives.[32,43] The anti-inflammatory agents are summarized in Table 3.

Other emerging agents

Clinical trials are currently evaluating the efficacy of anti-angiogenic therapies beyond anti-VEGF agents, such as squalamine.[19] Squalamine has shown improved visual outcomes in individuals with DME by suppressing several angiogenic factors, including VEGF, PDGF, and β-FGF. Research examining the combined use of squalamine and ranibizumab in individuals with DME is underway. Meanwhile, new therapeutic agents targeting the Ang-Tie2 signaling pathway have emerged. AKB-9778 [44] is a small-molecular substance that suppresses vascular endothelial-protein tyrosine phosphatase, promotes Tie2, and reduces vascular permeability; its efficacy in treating DME is being assessed in clinical trials. Similarly, nesvacumab,[19] an Ang-2 inhibitor that enhances Tie2 activation to lower vascular permeability, is undergoing evaluation when co-formulated with aflibercept, a VEGF inhibitor, in a phase 2 trial for DME. Additionally, RO6867461, a bispecific antibody that targets both Ang-2 and VEGF, is being investigated in DME.[19]

Brolucizumab, a 26 kDa single-chain antibody fragment, is administered by intravitreal injection and targets all isoforms of VEGF-A. Its effectiveness has also been assessed in the Phase 3 KITE and KESTREL trials comparing brolucizumab and aflibercept efficacy and durability in improving vision and anatomical outcomes in DME.[45,46] Similarly, KSI-301, a novel anti-VEGF antibody biopolymer conjugate, has demonstrated significant improvement in visual and anatomical outcomes in DME and non-proliferative diabetic retinopathy (NPDR), with ongoing Phase 3 trials (GLEAM and GLIMMER) aiming to validate its extended treatment intervals.[46,47] Gene therapy approaches such as RGX-314 (ALTITUDE trial) [48] and ADVM-022 (INFINITY trial) [49] are under investigation, offering the potential for long-term or even single-dose treatment. RGX-314 uses an AAV8 vector to deliver anti-VEGF genes via subretinal or suprachoroidal injection, while ADVM-022 employs a modified AAV2 vector encoding aflibercept, targeting DME disease activity.[48,49] Meanwhile, Port Delivery System (PDS) with ranibizumab provides a surgically implantable, refillable drug reservoir for sustained anti-VEGF delivery. Based on Phase 3 trials for DME and NPDR (PAGODA and PAVILION),[52] PDS-based continuous delivery may help slow the advancement of macular and peripheral retinal nonperfusion in patients with DME and DR. Current analyses also suggest that PDS can reduce macular leakage in DME patients.[46,50]

Other agents such as Faricimab (YOSEMITE and RHINE trial), targeting both VEGF-A and Angiopoietin-2, and OPT-302 (ShORe and COAST trial), inhibiting VEGF-C/D, show potential for addressing resistance to current anti-VEGF therapies.[52–54] Non-VEGF pathways are also being explored with THR-149 (plasma kallikrein inhibitor) and THR-687 (integrin receptor antagonist) in Phase 2 trials, providing innovative mechanisms of action.[54,55] These advancements reflect a diverse pipeline of treatments aiming to address unmet needs in DR and DME management.[46]

Emixustat, an oral small molecule, inhibits RPE65, reducing the availability of 11-cis retinal for opsin binding and thereby slowing the visual cycle. A Phase 2 placebo-controlled trial with 23 participants having PDR with or without DME reported slightly reduced VEGF concentrations in the emixustat group.

Table 3. Anti-inflammatory drugs for the treatment of DR.

Treatment	Mechanism	Clinical benefits
Triamcinolone acetonide	Suppresses pro-inflammatory and pro-angiogenic factors.	Reduces macular edema and stabilizes inflammation; limited benefits in pseudophakic eyes
Dexamethasone	Reduces inflammation and stabilizes the blood-retinal barrier.	Sustained macular edema reduction; improves visual acuity with fewer injections.
Fluocinolone acetonide	Long-term release to reduce inflammation and vascular permeability.	Durable control of chronic DME with improved visual outcomes over 3 years.

Table 4. Emerging agents under trial for diabetic retinopathy

Agents	Mechanism
Anti-angiogenic agents	
Squalamine	Inhibits VEGF, PDGF, and β-FGF
AKB-9778	Activates Tie2 to reduce vascular permeability
Nesvacumab	Ang-2 inhibitor enhancing Tie2 activation
RO6867461	Inhibits Ang-2 and VEGF
Brolucizumab	Targets all isoforms of VEGF-A
KSI-301	VEGF-A inhibitor
Faricimab	Targets VEGF-A and Ang-2
OPT-302	Inhibits VEGF-C and VEGF-D
THR-149	Inhibits plasma kallikrein
THR-687	Integrin receptor antagonist
Gene therapy	
RGX-314	AAV8 vector delivers anti-VEGF genes
ADVM-022	AAV2 vector encoding aflibercept
Visual cycle modulator	
Emixustat	Inhibits RPE65 to slow visual cycle and reduce VEGF levels

Although no notable differences were detected in central subfield thickness (CST) or best-corrected visual acuity (BCVA) for predetermined objectives, a post hoc analysis indicated a substantial decrease in CST among individuals administered emixustat relative to those receiving placebo.[46,56] Emerging pharmacological agents are outlined in Table 4.

Surgical treatment

Vitrectomy is a critical surgical procedure for advanced diabetic retinopathy, particularly in PDR cases complicated by persistent vitreous hemorrhage or tractional retinal detachment. The surgery removes the vitreous gel to clear blood and fibrous tissue, restoring retinal clarity and relieving traction that can distort the retina and impair vision. In tractional retinal detachment, vitrectomy helps by eliminating fibrovascular membranes and reducing traction. For DME cases with epiretinal membranes or vitreoretinal traction, vitrectomy reduces macular thickening and improves anatomical outcomes by addressing mechanical stress.[29,57]

Vitrectomy is often combined with internal limiting membrane (ILM) peeling to manage refractory DME. This approach targets pathologic structure, such as epiretinal membranes, that worsen macular edema and impair retinal function. ILM peeling aims to relieve traction and provide macular recovery. While anatomical improvements are common, visual outcomes vary, with about one-third of patients seeing improvements, while 20-30% may experience visual decline due to retinal damage or complications. Risks include cataract progression, retinal detachment, and infection, necessitating careful postoperative monitoring. Despite these risks, vitrectomy is a crucial option when other treatments fail.[29,57]

Vitrectomy reduces retinal thickness in diabetic edema, but visual gains are modest and inferior to anti-VEGF. [58] Although vitrectomy reduces central macular thickness more effectively than intravitreal triamcinolone acetonide at 12 months, it does not guarantee significant visual improvement.[59] Morphological gains are seen within six months compared to grid laser treatment, but long-term visual function shows no major differences. The presence of ILM detachment during surgery for DME without macular traction does not affect outcomes.[60] Recent research suggests cystotomy may provide long-term benefits for refractory cystoid macular edema, though larger studies are needed to confirm efficacy.[61] Further studies with larger samples are required to confirm its effectiveness. As with other vitrectomy procedures, there are associated risks, and patient selection should be approached with caution.[32]

Vitrectomy is advantageous for patients with DME who respond inadequately to anti-VEGF treatment and sub-Tenon triamcinolone acetonide. A study by Vikas et al.[62] found that pars plana vitrectomy with ILM peeling led to favorable anatomical results in cases with and without traction. The three-year results of vitrectomy in conjunction with intraoperative dexamethasone for non-tractional refractory DME were favorable, reducing the need for further injections.[63] These findings highlight vitrectomy's potential, especially with adjunctive therapies, as an

effective treatment for refractory DME.[57] Table 2 provides a summary of treatments that have gone through the trial phase.

CONCLUSION

Diabetes mellitus affects nearly half a billion people globally, placing a significant proportion at risk of vision impairment due to DR and its complications. DR pathogenesis involves complex, interrelated mechanisms including oxidative stress, inflammation, neurodegeneration, and neovascularization that collectively contribute to damage in retinal neurons, endothelial cells, pericytes, retinal pigment epithelium, and glial cells. Although current therapeutic interventions can yield favorable outcomes, limitations persist in their efficacy, safety profile, and accessibility. Emerging therapies, including novel pharmacological and surgical approaches, aim to address these gaps. Results from ongoing and future clinical trials may refine DR management and advance efforts to prevent vision loss. Further research is needed to clarify the pathogenesis of diabetic retinopathy and to support the effective translation of emerging evidence into clinical practice.

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Conflict of interest

All authors declare that they have no conflicts of interest.

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