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Original Article

Diabetic Retinopathy: A Comprehensive Review of Pathogenesis and Clinical Management

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ABSTRACT

Diabetic retinopathy is a leading cause of preventable vision loss globally, imposing significant socioeconomic burdens and escalating in prevalence parallel to the diabetes pandemic. The condition arises from a complex interplay of hyperglycaemia-induced vascular damage and neurodegeneration, driven by mechanisms involving oxidative stress, inflammation, and metabolic pathway dysregulation. The retina, with its accessible microvasculature, serves as a crucial indicator of broader systemic vascular health in diabetic patients, emphasizing the need for holistic management. Comprehensive management involves stringent control of blood glucose, blood pressure, and lipids, complemented by healthy lifestyle modifications. Regular, dilated eye examinations, adhering to established guidelines, are indispensable for early detection and timely intervention. Current therapeutic modalities, including laser photocoagulation, anti-VEGF intravitreal injections, and steroid implants, have significantly improved outcomes. Vitrectomy remains a vital surgical option for advanced complications. Future of Diabetic Retinopathy management is poised for transformative advancements, with promising research avenues in stem cell therapy, nanotechnology for targeted drug delivery, gene therapy to address underlying pathological pathways, and artificial intelligence for enhanced screening, diagnosis, and even prediction of systemic complications. These innovations aim to provide more effective, durable, and personalized treatment options, striving to preserve vision and improve quality of life for millions affected by diabetic retinopathy globally. This review delves into the multifaceted aspects of diabetic retinopathy, from its intricate pathogenesis to cutting-edge therapeutic advancements.

Keywords: Diabetic Retinopathy, Pathogenesis, Clinical Management

INTRODUCTION

Diabetic retinopathy (DR) is precisely defined as a medical condition where damage occurs to the retina due to diabetes, recognized as a principal microvascular disease linked to diabetes.[1] It stands as the primary cause of visual loss (VL) among diabetic patients and a major contributor to vision loss in individuals aged 20 to 74 years, making it a leading cause of blindness in developed countries.[1] The global prevalence of diabetes has surged dramatically over recent decades, with projections indicating a rise to 1.3 billion affected individuals by 2050.[1] This alarming increase in diabetes directly parallels a significant rise in DR, with approximately 34.6% of diabetic patients developing DR and 10.2% experiencing varying levels of vision impairment.[1] By 2045, the global DR population is estimated to reach 160 million [1], posing substantial challenges to quality of life and exacerbating the global healthcare burden.[1] The escalating global burden of DR is not merely a medical challenge but a significant public health and socioeconomic crisis. The sheer scale of projected diabetes cases directly translates to a massive increase in DR cases. Given that DR is a leading cause of preventable blindness and disability, its widespread occurrence will inevitably strain healthcare systems, reduce workforce productivity, and necessitate significant societal support for affected individuals, extending its impact far beyond clinical ophthalmology. This highlights the need for systemic, broad-based strategies rather than just individual patient management.[2] Diabetic retinopathy is one of several ocular complications associated with diabetes, which also include cataracts (clouding of the eye's lens) and glaucoma (increased fluid pressure inside the eye leading to optic nerve damage).[3] Diabetes impacts the human body in various ways, primarily by

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affecting blood vessels throughout the body.[4] In the retina, prolonged high blood sugar levels can lead to blockages in small blood vessels, causing fluid leakage or bleeding, which results in damage to the eye and vision impairment.[4] DR is a sentinel microvascular complication, often indicative of broader systemic vascular damage in diabetic patients. The specific and early damage to the small retinal blood vessels in DR suggests that the retina acts as a visible "window" into the systemic microvascular health of a diabetic patient. The presence and severity of DR can therefore serve as a strong indicator of the overall progression of diabetes-related vascular complications throughout the body, underscoring the importance of comprehensive diabetes management beyond just ocular health.

II. Epidemiology and Global Burden

Globally, approximately 34.6% of diabetic patients develop DR.[1] A comprehensive systematic review estimated the global prevalence of DR among individuals with diabetes at 22.27% (95% confidence interval [CI], 19.73%-25.03%), with vision-threatening DR (VTDR) at 6.17% (95% CI, 5.43%-6.98%) and clinically significant macular edema (CSME) at 4.07% (95% CI, 3.42%-4.82%).[5] Another meta-analysis estimated the current global prevalence of DR to be around 103 million individuals, projected to rise to 161 million by 2045.[2] The condition affects up to 80% of individuals who have had both type 1 and type 2 diabetes for 20 years or more.[6] In the United States, DR accounts for 12% of all new cases of blindness annually and is the leading cause of blindness in people aged 20 to 64.[6] In China, the number of years lived with disability (YLDs) attributed to DR was 86,317 in 2021, with a prevalence of 1.37 million cases. The age-standardized YLD rate (ASYR) increased from 3.21 per 100,000 people in 1990 to 4.04 per 100,000 in 2021.[1] By 2045, the number of individuals with diabetes in China is projected to reach 174 million, with approximately 16.3% developing DR and 3.2% experiencing vision-threatening conditions.[1] Regional disparities in DR prevalence are notable. The prevalence of DR was highest in Africa (35.90%) and North America and the Caribbean (33.30%), and lowest in South and Central America (13.37%).[5] Furthermore, projections to 2030 indicate that rates of increase in DR prevalence in middle- to low-income regions, such as the Western Pacific, the Middle East, North Africa, and Africa, range from 20.6% to 47.2%, significantly outpacing projected rates in high-income regions like Europe and North America.[2] This suggests a disproportionate effect on developing countries, where healthcare infrastructure may be less equipped to handle the rising burden.[2] The global burden of DR is expected to remain high through 2045, disproportionately affecting countries in the Middle East and North Africa and the Western Pacific.[5] This demographic shift in disease burden, from traditionally high-income countries to developing nations, underscores a critical public health challenge. The increasing prevalence of diabetes in developing countries, coupled with potentially limited access to specialized eye care, means that a larger proportion of the global population will be at risk of severe vision loss from DR. This necessitates the development of broad, system-wide strategies, including improved understanding of epidemiology, risk factors, and public health challenges, along with evolving screening strategies leveraging new technologies, to effectively manage and mitigate the impact of this growing epidemic.[2]

III. Pathophysiology

Diabetic retinopathy is fundamentally caused by prolonged high blood glucose levels damaging the small blood vessels and neurons of the retina.[6] The earliest changes leading to DR include narrowing of retinal arteries and reduced retinal blood flow, followed by dysfunction of inner and outer retinal neurons.[6] Progression of DR is accompanied by pericyte loss, increased blood vessel permeability, and altered retinal blood flow, all of which reduce oxygen delivery to the retina.[6]

A. Cellular and Molecular Mechanisms of Retinal Vascular Damage

The microvasculature of the retina responds to hyperglycaemia through a number of biochemical changes, leading to endothelial dysfunction, increased vascular permeability, and eventual microvascular occlusion.[7] Key pathological features include pericyte loss, thickening of the basement membrane, microaneurysm formation, neovascularization, and disruption of the blood–retinal barrier.[8] Several interrelated biochemical pathways are implicated:

- **Oxidative Stress:** Hyperglycaemia induces oxidative stress, characterized by an imbalance between the formation and removal of free radicals.[9] Excessive reactive oxygen species (ROS) accumulation damages retinal vessels and contributes to mitochondrial damage, cellular apoptosis, inflammation, and lipid peroxidation.[10] This process is exacerbated by hyperglycaemia-mediated epigenetic modifications that repress antioxidant defence systems.[10] Oxidative stress is a critical contributor to DR pathogenesis and is closely associated with pathological changes.[11]

- **Inflammation:** Hyperglycaemia activates macrophages and microglia, promoting the release of pro-inflammatory cytokines such as IL-1β, IL-6, TNF-α, and ICAM-1, which stimulate NF-κB and HIF-1α signaling.[11] There is a positive feedback loop where free radicals increase inflammatory mediators, and inflammation increases free radical production.[9] This inflammatory response plays a prominent role in DR pathogenesis.[7]

- **Polyol Pathway Activation:** Excess glucose is metabolized via the polyol pathway to sorbitol, which accumulates inside cells, inducing osmotic damage.[12] This pathway also reduces NADPH availability, increasing cellular sensitivity to oxidative stress.[12]

- **Advanced Glycation End-products (AGEs) Formation:** High glucose levels significantly increase AGEs formation.[8] AGEs cross-link proteins, altering their structure and function in basement membranes and blood vessel walls.[12] Activation of AGEs receptors induces pro-oxidant and pro-inflammatory cascades, exacerbating oxidative stress and leukocyte adhesion, and is correlated with pericyte loss.[12]

- **Protein Kinase C (PKC) Activation:** Increased glycolysis activity during hyperglycaemia elevates diacylglycerol (DAG) synthesis, activating the PKC pathway.[8] PKC activates mitogen-activated protein kinase (MAPK) factors, enhancing expression of stress-related proteins and vascular function mediators. Specifically, the PKC-β isoform increases VEGF expression, and PKC activation drives overexpression of NADPH oxidase and NFκB, exacerbating oxidative stress and inflammation.[8]

- **Hexosamine Pathway Flux:** In this pathway, fructose-6-phosphate is converted into UDP-GlcNAc, which affects the expression of multiple factors involved in DR pathophysiology, representing a key regulatory mechanism of glucose-responsive gene transcription.[12]

- **Renin–Angiotensin System (RAS) Activation:** The RAS also contributes to the mechanisms of diabetes-induced retinal damage.[7]

B. Neural Tissue Damage and Molecular Pathways

Diabetic retinopathy is increasingly recognized as a neurodegenerative and vascular pathology.[11] Neurodegeneration has been shown to be present in diabetic human retinas at structural, functional, and molecular levels, even in the absence of clinically visible microvascular abnormalities.[13] This highlights that DR is not solely a vascular disease but also involves significant neuronal damage from its early stages. This understanding is crucial because it suggests that interventions focused purely on vascular repair might not fully address the disease's progression or restore vision, necessitating a more holistic approach that considers neural protection. Major forms of retinal neurodegeneration include apoptosis (programmed cell death) and glial activation.[13] Glial cells, when activated, proliferate, migrate, phagocytose, and secrete biological factors, leading to neuronal damage through phagocytosis, toxin production, and induction of apoptosis.[13]

- **Glutamate Excitotoxicity:** An imbalance in glutamate production and/or metabolism leads to overexpression of excitatory proteins like glutamate and NMDA receptors in the retina and vitreous.[13] Activation of NMDA receptors causes calcium influx, leading to caspase release and apoptosis of retinal neurons.[13]

- **Oxidative Stress:** Reactive oxygen species (ROS), such as nitric oxide (NO), are overexpressed in hyperglycaemia through PKC

pathway activation and increased NADH oxidases.[13] While NO has physiological roles, its release from retinal glial cells can induce apoptosis of neuronal cells.[13] The oxidative stress resulting from ROS and mitochondrial dysfunction in diabetic retinas is a significant factor in neuronal apoptosis.[13]

The interplay between vascular and neural damage is complex. Microvascular occlusion, a consequence of vascular damage, leads to retinal ischemia, which further promotes neovascularization and the formation of intraretinal microvascular abnormalities (IRMAs).[12] This continuous cycle of damage and compensatory, yet pathological, responses underscores the progressive nature of DR.

IV. Clinical Classification and Presentation

Diabetic retinopathy is broadly classified into two main types: Non-proliferative Diabetic Retinopathy (NPDR) and Proliferative Diabetic Retinopathy (PDR).[4] The distinguishing feature between these two categories is the presence (PDR) or absence (NPDR) of abnormal new blood vessels (neovascularization) on the retina, optic disc, or iris.[14]

A. Non-proliferative Diabetic Retinopathy (NPDR)

NPDR represents the early stages of DR, characterized by increased vascular permeability and capillary occlusion.[12] In this form, new blood vessels are not growing (non-proliferating).[15] The walls of the retinal blood vessels weaken, leading to tiny bulges called microaneurysms, which may leak fluid and blood into the retina.[15] Larger retinal vessels can also dilate and become irregular.[15] NPDR is further categorized into mild, moderate, and severe stages based on the extent of retinal changes.[4]

- **Mild NPDR:** This is the earliest stage, marked by the presence of only a few microaneurysms.[4] Patients are typically asymptomatic, with no noticeable effect on vision.[6] However, it signals that diabetes-related damage has begun.[16]

- **Moderate NPDR:** As the disease progresses, there is an increased number of microaneurysms and dot-and-blot haemorrhages.[4] Some blood vessels nourishing the retina become blocked, disrupting blood flow and depriving the retina of nutrients.[4] Cotton wool spots and hard exudates may also be present.[14] Vision may become blurry if fluid accumulates in the macula.[4]

- **Severe NPDR:** This stage is characterized by more extensive damage, with many blood vessels blocked, significantly reducing blood flow to several retinal areas.[4] It is often identified by the "4-2-1 rule": severe retinal haemorrhages and microaneurysms in all four quadrants, venous beading in two or more quadrants, or intraretinal microvascular abnormalities (IRMA) in one or more quadrants.[4] The lack of blood supply triggers signals for the body to grow new blood vessels.[3] At this stage, there is a high chance of irreversible vision loss.[17]

B. Proliferative Diabetic Retinopathy (PDR)

PDR is the most advanced and severe stage of diabetic retinopathy.[4] It is characterized by insufficient oxygen supply to the retina, which triggers the growth of new, abnormal, and fragile blood vessels (neovascularization) on the surface of the retina or into the vitreous gel.[4] These new vessels, by themselves, do not cause symptoms or vision loss, but their thin, fragile walls make them prone to leakage.[3] If these abnormal vessels leak blood, severe vision loss and even blindness can result.[4] Minor bleeding can cause dark floating spots (floaters), while major bleeding can completely block vision (vitreous haemorrhage).[6] Scar tissue from the growth of new blood vessels can also pull the retina away from the back of the eye, leading to retinal detachment, which manifests as sudden dark spots, flashes of light, or blurred vision.[6] If these new blood vessels interfere with the normal fluid outflow from the eye, pressure can build, damaging the optic nerve and resulting in glaucoma.[15]

C. Diabetic Macular Edema (DME)

Diabetic macular edema (DME) is a critical complication that can occur at any stage of DR, from mild NPDR to PDR, though it is more frequent as DR severity increases.[3] DME is characterized by the accumulation of excess fluid in the macula, the central part of the retina responsible for sharp, straight-ahead

vision and fine details.[6] This fluid leakage causes the macula to swell, blurring vision.[3] Symptoms of DME can range from mildly blurred vision to severe loss of central visual field.[6] Other symptoms include distorted vision, new color blindness or faded colors, night blindness, floaters, blind spots, and difficulty reading.[18] Importantly, DME can develop without noticeable symptoms in its early stages.[3] Left untreated, approximately 30% of those with macular swelling experience vision disruption over 3–5 years.[2] DME is the most common cause of vision loss in people with diabetic retinopathy.[6] DME has an inflammatory component, with upregulation of various chemokines and cytokines, including vascular endothelial growth factor (VEGF), interleukins (ILs), matrix metalloproteinases, and tumour necrosis factor (TNF).[19] This leads to increased inflammation, oxidative stress, and vascular dysfunction, altering the homeostasis of the neurovascular unit.[19]

D. Classification Systems

Several classification systems have been developed to stage DR and DME, aiding in prognosis and treatment decisions. The Early Treatment of Diabetic Retinopathy Study (ETDRS) classification is considered the gold standard.[20] It grades fundus lesions such as haemorrhages/microaneurysms (H/Mas), venous beading and loops, hard exudates, IRMAs, and neovascularization from standard 7-field 30° fundus photographs.[21] The ETDRS system provides a detailed 13-level severity scale, ranging from no retinopathy to severe vitreous hemorrhage.[21] While comprehensive, the ETDRS system is complex, limiting its usefulness for daily clinical practice.[22] A simplified version, the International Clinical Disease Severity Scale for DR and DME, has been developed and endorsed by international authorities, including the World Health Organization.[23] This scale is simpler, based on clinical examination and the ETDRS 4:2:1 rule, and does not require specialized imaging like OCT or fluorescein angiography for initial classification.[23] It classifies retinopathy into five stages (no apparent, mild NPDR, moderate NPDR, severe NPDR, proliferative DR) and maculopathy as either absent or present (mild, moderate, severe).[24]

V. Risk Factors

The development and progression of diabetic retinopathy are influenced by a combination of systemic and genetic factors, beyond the primary driver of glycaemic control.

A. Systemic Risk Factors

- **Duration of Diabetes:** The longer a person has diabetes, the higher their chances of developing DR.[6] For instance, up to 80% of individuals with type 1 and type 2 diabetes develop some degree of retinopathy after 20 years or more.[6]

- **Poor Glycaemic Control:** Chronically high blood sugar, measured by high HbA1c levels, is the most significant and dominant risk factor for DR.[6] A decrease of about 10% in HbA1c can result in a 39% decrease in the risk of DR progression.[25] Both chronically high and highly variable blood sugar levels are associated with DR.[6]

- **High Blood Pressure (Hypertension):** Elevated blood pressure is a significant risk factor for DR development and progression.[6] While intensive blood pressure control reduces the risk of DR development, its impact on the progression of existing DR compared to less stringent measures is less clear.[25] However, managing hypertension is crucial for overall diabetes management.[26]

- **Dyslipidaemia (Abnormal Blood Lipids):** Elevated serum cholesterol and triglyceride levels have been implicated as risk factors for DR.[6] While studies on statin and fibrate treatment effects specifically on DR have mixed results, lipid control is beneficial for overall diabetes management and cardiovascular health.[27] Hard exudates in DME are thought to be a result of lipoproteins leaking from retinal capillaries.[27]

- **Pregnancy:** Pregnancy significantly increases the risk for the development and progression of DR in women with pre-existing type 1 or type 2 diabetes.[15] Close monitoring and early eye examinations are recommended during and after pregnancy.[15]

- **Tobacco Use:** Smoking increases the risk of various diabetes complications, including DR.[6]

- **High Body Mass Index (BMI) / Overweight and Obesity:** Overweight and obesity are additional risk factors for DR, necessitating management beyond cardiovascular concerns.[6]

- **Kidney Disease (Nephropathy):** Kidney disease is a minor risk factor that can exacerbate DR.[6]

- **Ethnicity:** Being Black, Hispanic, or Native American can increase the risk of developing DR.[15] Hispanics and Middle Easterners with diabetes are more likely to have DR compared with Asians.[5]

B. Genetic Risk Factors

Genetic susceptibility influences not only the risk of DR but also the pace and severity of its progression.[28] DR is considered a polygenic disorder, with twin and familial aggregation studies documenting clear familial clustering.[28] Heritability has been estimated to be as high as 27% for any DR and 52% for proliferative diabetic retinopathy (PDR).[29] This strong familial component suggests that genetic background plays a substantial role in an individual's predisposition to the disease. Several genes and pathways have been identified as key players in DR pathogenesis:

- **Vascular Endothelial Growth Factor A (VEGFA):** Polymorphisms in VEGFA, such as rs699947 and rs2010963, are associated with a higher risk of DR.[30] VEGFA is pivotal in promoting angiogenesis, the formation of new blood vessels, which is a hallmark of PDR.[30]

- **Tumour Necrosis Factor-alpha (TNF-α):** Genetic polymorphisms in the TNF-α gene, such as the -308G/A polymorphism (rs1800629), are linked to higher TNF-α production and increased DR susceptibility.[30] TNF-α is a potent pro-inflammatory cytokine crucial to DR pathogenesis.[30]

- **Other Genes:** Other genes with a putative role in DR include aldose reductase (ALR), receptor for advanced glycation end-products (RAGE), and genes in the renin-angiotensin system (RAS).[29]

- **Gender:** Studies suggest that gender influences the incidence and progression of diabetes, as well as the risk, severity, and treatment response of DR.[30] Epidemiological studies indicate that men are more likely than women to develop DR under poor diabetes management.[30] However, the influence of gender on the severity of DR yields varied findings, with some studies showing men have a higher risk of progressing to advanced DR stages, while others find certain subgroups of women more prone to specific DR forms like DME.[30] Gender may also influence DR treatment effectiveness, potentially due to sex hormones, genetic background, and lifestyle interactions.[30] The genetic component of DR means that even with good glycaemic control, some individuals may still be at higher risk due to their inherited predispositions. This implies that personalized screening intervals based on familial risk factors may aid in early detection and intervention, and future research should explore how gender influences DR risk and treatment responses through biological mechanisms, hormones, genetic factors, and lifestyle.[30]

VI. Diagnostic Methods

Early detection of diabetic retinopathy is crucial for preventing vision loss, as symptoms often do not appear until the disease has advanced.[31] A comprehensive dilated eye exam is the gold standard for diagnosing DR and monitoring patients at risk.[32] This involves dilating the pupils to allow the eye care professional a better view inside the eye, looking for abnormalities like leaking blood vessels, retinal swelling (macular edema), pale fatty deposits, damaged nerve tissue, and changes to blood vessels.[3] Beyond the clinical exam, several advanced imaging techniques are employed to detect, classify, and monitor DR and its complications:

A. Fundus Photography

Color fundus photography is a widely used tool for documenting retinopathy, screening for diabetic eye disease, detecting progression, and monitoring treatment response.[33] It is also useful for patient counselling, allowing them to visualize their condition.[34]

- **Standard Fundus Photography:** Traditionally, this method captures a 30° field of view of the

posterior pole, including the macula and optic nerve.[35] While easy to use and widely available, it cannot confirm clinically significant macular edema (CSME) and may miss fine details or be limited by media opacities.[34] The gold standard for DR detection has been stereoscopic color fundus photography in 7 standard fields (30°) as defined by the ETDRS group.[33]

- **Widefield Fundus Photography:** This newer technology can image the peripheral retina, capturing up to a 200° field of view (approximately 82.5% of the total retinal surface) in a single photograph, even with an undilated pupil.[35] Ultra-widefield (UWF) imaging has increased the identification of DR by 17%, with peripheral lesions suggesting greater disease severity in 9% of cases compared to standard imaging.[36] It also reduces ungradable images and evaluation time.[36] While offering more thorough documentation, widefield imaging can have limitations such as image distortion, eyelash artifacts, false color representation, and high equipment costs.[34]

- **Digital Fundus Photography:** This has largely replaced film-based photography, offering immediate review, easy magnification, and image enhancement.[34] Telemedicine approaches often utilize digital retinal imaging, where images are taken at one site and transmitted for remote interpretation by trained graders or artificial intelligence (AI) algorithms.[33] This approach is cost-effective for screening large populations and can increase access to DR screening, especially in resource-limited settings.[25]

B. Optical Coherence Tomography (OCT) and OCT Angiography (OCT-A)

Optical Coherence Tomography (OCT) is a non-invasive imaging method that uses reflected light to create cross-sectional, detailed two- and three-dimensional images of the retina.[36] It has revolutionized ophthalmology by providing detailed information about histological changes and allowing quantitative measurement of retinal thickness and volume, as well as structural changes in cellular layers.[36]

- **Role in DR and DME:** OCT is invaluable for diagnosing and monitoring DR and DME.[37] It can detect retinal and macular thickening, fluid accumulation (edema), exudates, photoreceptor atrophy, and hemorrhage.[36] OCT helps in understanding vitreoretinal relationships and the internal architecture of the retina in diabetes, greatly influencing therapeutic decisions for DME.[36]

- **OCT Angiography (OCT-A):** A relatively recent innovation, OCT-A visualizes the retinal microvasculature and choriocapillaris based on the motion contrast of circulating blood cells, without the need for dye injection.[36] It provides depth-resolved visualization of microvasculature at different retinal layers.[38] OCT-A can quantify microvascular alterations and detect classical DR features like microaneurysms, IRMA, and neovascularization.[38] It also has a promising role in identifying preclinical microvascular abnormalities that precede clinically detectable DR, offering insights into early-stage pathophysiology.[38] This non-invasive nature allows for repeated examinations, making it an ideal technique for regular clinical practice where fluorescein angiography might be too invasive or expensive.[38]

C. Fluorescein Angiography (FA)

Fluorescein angiography is an imaging test that uses a fluorescent dye injected into a vein (typically in the arm) to highlight blood vessels in the retina.[39] A special camera with a blue flash then takes a series of pictures as the dye circulates, revealing changes in the structure or function of retinal blood vessels.[39]

- **Role in DR and DME:** FA is considered the gold standard for evaluating the retinal vasculature in diabetic eye disease.[34] It is particularly useful for detecting vascular leakage, areas of capillary nonperfusion (ischemia), and neovascularization.[35] It helps diagnose or monitor conditions like diabetes-related retinopathy and cystoid macular edema.[39]

- **Limitations:** While highly effective, FA is an invasive procedure, relatively expensive, and

time-consuming, making it less ideal for regular, routine screening compared to non-invasive methods like OCT-A.[38]

D. B-scan Ultrasonography

Ocular B-scan ultrasound is an imaging technique that uses high-frequency sound waves to create images of the retina and surrounding structures.[40] It is particularly valuable for diagnosing and managing intraocular disorders when the ocular media are opaque (e.g., due to dense cataracts or vitreous haemorrhage), where light-based imaging methods are limited.[40]

- **Role in DR Complications:** B-scan ultrasound is used to identify complications of DR, including vitreous haemorrhage, vitreous traction, and retinal detachment.[40] It can also help differentiate between different types of retinal detachments and characterize other intraocular pathologies.[40] Studies have shown high sensitivity (98.9%) and specificity (85.7%) for ophthalmic ultrasound in detecting causes of low vision in diabetic patients.[41] It remains a useful part of ophthalmic examination for the detection and evaluation of DR complications, especially in cases of poor posterior eye segment visualization.[41]

VII. Treatment Modalities

Treatment for diabetic retinopathy is largely dependent on the type and severity of the condition, aiming to slow or halt progression and preserve vision.[42] Early intervention is crucial, as it significantly improves the chances of saving vision.[31]

A. Systemic Management

Controlling systemic factors is paramount in the management and prevention of DR progression.[26]

- **Glycaemic Control:** Strict control of hyperglycaemia is essential.[26] Good glycaemic control from diagnosis is beneficial in preventing onset and delaying progression of DR.[26] A decrease of about 10% in HbA1c can reduce DR progression risk by 39%.[25] For most people with diabetes, the HbA1c goal is typically under 7% (or 48 mmol/mol).[43]
- **Blood Pressure Control:** Management of high blood pressure is critical, as hypertension often coexists with diabetes and is a significant risk factor for DR.[26] A target blood pressure of no more than 140/80mmHg, or less than 130/80mmHg if complications like eye damage are present, is generally advised.[44]
- **Lipid Control:** Elevated serum cholesterol and triglyceride levels are risk factors for DR.[27] While the direct effect of lipid-lowering medications on DR progression has mixed results, fenofibrate has shown benefit on both proliferative disease and maculopathy, potentially beyond its lipid-lowering effect.[26] A healthy total cholesterol level is typically below 4mmol/l.[44]
- **Other Systemic Approaches:** Research has explored other systemic interventions, including anti-platelet agents (with no proven efficacy for DR), PKC inhibitors (e.g., ruboxistaurin, showing some beneficial effects but not FDA-approved), and suppression of GLUT1 (a glucose transporter, a potential target for local and systemic treatment).[26]

B. Laser Photocoagulation

Laser treatment (photocoagulation) has been a cornerstone of DR management for decades.[8] It works by using laser light absorbed by the retinal pigment epithelium (RPE) and choroid, converting energy to heat, causing local retinal cell death and coagulative necrosis, which eventually scars.[45]

- **Focal Laser Treatment (for DME):** This procedure stops or slows the leakage of blood and fluid in the eye by treating leaks from abnormal blood vessels with laser burns.[46] It is typically performed in a single session in an outpatient setting.[42] While it may not restore vision to normal if blurred by macular edema, it significantly reduces the chance of worsening.[42] Subthreshold diode micropulse (SDM) laser uses pulsed laser at high speed to treat ocular tissue without visible burns, initially used for DME.[47]
- **Panretinal Photocoagulation (PRP) (for PDR):** Also known as scatter laser treatment, PRP shrinks abnormal new blood vessels by applying

scattered laser burns to areas of the retina away from the macula.[46] This reduces the retina's demand for oxygen and prevents further abnormal vessel growth and scar tissue formation.[47] PRP is usually done in two or more sessions.[42] The Diabetic Retinopathy Study (DRS) demonstrated that PRP reduced the risk of severe visual loss (SVL) by more than 50% in patients with PDR.[45] While effective, PRP can cause side effects such as some loss of peripheral or night vision.[42] The ETDRS advised against initiating scatter photocoagulation in mild NPDR to balance adverse effects against minimal benefits.[45]

C. Anti-VEGF Injections

Vascular endothelial growth factor (VEGF) inhibitors are injected into the vitreous of the eye to stop the growth of new blood vessels and decrease fluid buildup.[8] These agents have demonstrated clinical efficacy in reducing vascular leakage and neovascularization.[8]

- **For DME:** Anti-VEGF therapy is generally the first-line treatment for DME, especially when visual acuity is impaired and DME is subfoveal.[48] FDA-approved drugs include faricimab-svoa (Vabysmo), ranibizumab (Lucentis), and aflibercept (Eylea), with bevacizumab (Avastin) used off-label.[42] Studies have shown anti-VEGF therapy to result in significant visual acuity gains, outperforming laser therapy for DME.[49] A new implantable device, Susvimo (ranibizumab), continuously delivers medicine, reducing the need for monthly injections to twice a year.[48]

- **For PDR:** Anti-VEGF agents also reduce the severity of DR and effectively treat PDR.[32] They can help shrink new blood vessels in PDR.[50]

- **Considerations:** Injections typically cause mild discomfort and have possible side effects like increased intraocular pressure and infection.[42] They require repeated administration.[42] While effective, some patients may not respond optimally, suggesting that other cytokines besides VEGF play a role in DME pathogenesis.[51]

D. Steroid Implants

Corticosteroids, delivered via intravitreal injections or implants, are used in the management of DME, particularly in cases resistant to anti-VEGF therapy or in vitrectomized eyes.[50] They work by blocking VEGF production and other inflammatory cytokines, inhibiting leukostasis, and enhancing the barrier function of vascular endothelial cell tight junctions.[52]

- **Types and Efficacy:** Currently available corticosteroids include triamcinolone acetonide (TA), the dexamethasone (DEX) intravitreal implant (Ozurdex®), and the fluocinolone acetonide (FA) intravitreal implant.[51] DEX implants have shown efficacy in improving visual acuity and reducing central retinal thickness in DME patients, with maximum effect around 2 months post-injection.[52]

- **Advantages and Disadvantages:** A main advantage of corticosteroids is their longer duration of action compared to anti-VEGF injections, reducing treatment burden.[51] They can be considered first-line treatment in pseudophakic eyes, previously vitrectomized eyes, and for patients who have difficulty maintaining frequent appointments.[51] However, common adverse events include cataract formation/progression and ocular hypertension.[51]

E. Vitrectomy

Vitrectomy is a surgical procedure for advanced stages of diabetic retinopathy, typically performed to correct complications like vitreous haemorrhage and tractional retinal detachment.[42]

- **Procedure:** The surgeon makes tiny incisions in the eye to remove blood, scar tissue, or the cloudy vitreous gel, which is then replaced with fluid, silicone oil, or gas.[42] Laser treatment or medication may also be administered during the surgery.[42]

- **Indications:** Vitrectomy is indicated when blood or scar tissue significantly impacts the retina or vitreous, especially in proliferative diabetic retinopathy where abnormal blood vessels leak into the vitreous or form scar tissue that displaces or tears the retina.[53] It is

considered an effective and safe treatment option for PDR, with generally positive long-term outcomes.[53]

- **Recovery and Risks:** Vision may initially be blurry after surgery, gradually improving over several months.[53] Possible side effects include cataract development, further bleeding, retinal detachment, fluid build-up in the cornea, and eye infection.[53]

VIII. Prevention and Management Strategies

Preventing the onset and progression of diabetic retinopathy hinges on a multi-faceted approach involving comprehensive diabetes management, regular eye screenings, and lifestyle modifications.

A. Comprehensive Diabetes Management

Effective management of diabetes is the foundation for preventing DR.[3] This involves:

- **Blood Sugar Control:** Consistent monitoring and maintaining blood sugar levels within target ranges are critical.[15] The HbA1c test, reflecting average blood sugar over 2-3 months, should ideally be under 7% (48 mmol/mol) for most individuals with diabetes.[15] Continuous glucose monitoring devices and mobile health applications can significantly enhance glycaemic control and self-management capabilities.[54]

- **Blood Pressure Control:** Maintaining healthy blood pressure (e.g., below 140/80mmHg, or less than 130/80mmHg with complications) is crucial.[15]

- **Cholesterol Management:** Keeping cholesterol levels under control (e.g., total cholesterol below 4mmol/l) reduces the risk of DR.[15]

- **Medication Adherence:** Taking prescribed oral diabetes medications or insulin as directed is vital for blood sugar control.[15] Medications for blood pressure (e.g., ACE inhibitors) and cholesterol (e.g., statins) may also be prescribed.[44]

B. Lifestyle Modifications

Adopting healthy lifestyle choices can significantly reduce the risk of developing DR or slow its progression.[44]

- **Healthy, Balanced Diet:** Emphasize fruits, vegetables, and whole grains, while cutting down on salt, fat, and sugar.[44] Nutrients like omega-3 fatty acids, zinc, and vitamins C and E are particularly beneficial for eye health.[55]

- **Regular Physical Activity:** Aim for at least 150 minutes of moderate-intensity activity per week, such as walking or cycling.[15] Regular exercise enhances insulin sensitivity and promotes healthy blood circulation, vital for optimal eye function.[55]

- **Weight Management:** Losing weight if overweight or obese and maintaining a healthy BMI (18.5-24.9) is crucial, as it improves insulin resistance and blood sugar control.[18]

- **Smoking Cessation:** Quitting smoking or other tobacco use dramatically lowers the risk of DR and other diabetes complications.[15]

- **Moderate Alcohol Consumption:** Not exceeding recommended alcohol limits is also advised.[44]

- **Stress Management:** Chronic stress can exacerbate diabetes-related complications, including DR. Incorporating relaxation techniques can contribute to overall well-being.[55]

C. Regular Eye Screenings and Guidelines

Even with well-controlled diabetes, regular eye exams are essential for early detection, as DR often has no symptoms in its early stages.[31] Timely detection allows for early intervention, significantly improving treatment effectiveness and preserving vision.[31]

- **Screening Frequency:**

  - **Type 1 Diabetes:** First retinal exam 3-5 years after diagnosis, then annually.[25]

  - **Type 2 Diabetes:** First retinal exam at the time of diagnosis, then at least annually thereafter.[25]

- **Pregnancy (with pre-existing diabetes):** First retinal exam soon after conception and early in the first trimester, with close follow-up throughout pregnancy and up to 1 year postpartum, as DR can progress rapidly during pregnancy.[15] An eye exam is not required for gestational diabetes.[56]

- **Adjusted Intervals:** If annual exams show no DR and glycaemic indicators are within goal, examinations can extend to every 1-2 years. However, intervals should be adjusted based on other risk factors like progression of retinopathy, advanced baseline retinopathy, uncontrolled hyperglycaemia, or DME.[25]

- **Screening Methods:**

- **Dilated Fundus Examination:** Considered the gold standard, performed by an ophthalmologist or optometrist.[32]

- **Retinal (Fundus) Photography:** Including 30° to wide field, monophotography or stereophotography, and dilated or undilated photography.[57] Digital retinal imaging, often with remote interpretation (tele-retina), is a cost-effective alternative to increase access to screening, especially in resource-limited settings.[25] However, retinal photographs cannot substitute for in-person follow-up once abnormalities are detected.[25]

- **Optical Coherence Tomography (OCT):** Can be used with retinal examination.[57]

- **Visual Acuity Screening:** Includes refracted or presenting visual acuity examination using charts.[43]

- **Tonometry:** Measures eye pressure to screen for glaucoma.[43]

The International Council of Ophthalmology (ICO) and American Diabetes Association (ADA) guidelines provide specific recommendations for screening and referral based on DR severity and resource settings.

Table 1: ICO/ADA 2018 DR Screening and Referral Guidelines for High Resource Settings [57]

Classification	Re-examination or Next Screening Schedule	Referral to Ophthalmologist
Diabetic Retinopathy (DR)		
No apparent DR	1–2 yrs	Not required
Mild non-proliferative DR	6–12 mos	Not required
Moderate non-proliferative DR	3–6 mos	Required
Severe non-proliferative DR	<3 mos	Required
Proliferative DR	<1 mo	Required
Diabetic Macular Edema (DME)		
Non–center-involving DME	3 mos	Required
Center-involving DME	1 mo	Required

Table 2: ICO/ADA 2018 DR Screening Follow-up Guidelines for Low-Intermediate Resource Settings [57]

Classification	Re-examination or Next Screening Schedule	Referral to Ophthalmologist
Diabetic Retinopathy (DR)		
No apparent DR	1–2 yrs	Not required
Mild non-proliferative DR	1–2 yrs	Not required
Moderate non-proliferative DR	6–12 mos	Required
Severe non-proliferative DR	<3 mos	Required
Proliferative DR	<1 mo	Required
Diabetic Macular Edema (DME)		
Non–center-involving DME	3 mos	Not required (referral recommended if laser sources available)
Center-involving DME	1 mo	Required

D. Patient Education and Adherence

Patient education is crucial for improving adherence to DR screening guidelines and management plans.[31] Factors influencing adherence include knowledge of the connection between DR and diabetes, the importance of screening, care provider recommendations, and pre-booked appointments.[31] Common barriers to adherence include limited awareness about diabetes and eye complications, belief that screening is unnecessary if vision is good, direct and indirect costs (e.g., travel), distance from centres, discomfort from dilating drops, the burden of multiple appointments, fear of laser treatment, and guilt surrounding poor glycaemic control.[58]

Strategies to improve adherence include:

- **Intensive Patient Education:** Health workers should offer programs covering diabetes, potential blindness, and eye health, emphasizing the importance of regular retinal checks.[58]
- **Personalized Communication:** Screeners or ophthalmologists can show patients their retinal images to highlight changes, encouraging future attendance and good glycaemic control.[58] Information should be available in preferred languages and large print.[58]
- **Support Systems:** Encourage allied health professionals to personally recommend annual retinal checks. Support patients, especially those with poor control, to find solutions to challenges without blame.[58] Family support also facilitates adherence.[31]
- **Practical Arrangements:** Minimize costs and travel time, locate screening centers with good transport links, and offer flexible appointment hours.[58] Consistent location and routine can increase familiarity and compliance.[58]
- **Follow-up for Non-attendees:** Instead of discharging patients who miss appointments, they should be identified and contacted personally to understand reasons for poor attendance and find solutions.[58] Reliable reminder systems, such as text messages, are beneficial.[58]

IX. Future Directions

The landscape of diabetic retinopathy treatment and management is rapidly evolving, driven by ongoing research into new therapeutic approaches and advanced technologies.

A. Research Advances in New Treatments

Current treatments primarily target advanced stages of DR, but research is exploring interventions that address underlying causes and improve visual recovery potential.[8]

- **Targeting Key Biological Pathways:** Beyond anti-VEGF therapies, new research focuses on fibroblast growth factor, platelet-derived growth factor, and the Wnt/β-catenin pathway to reduce retinal vascular leakage and abnormal neovascularization.[54] PPARα activation and modulation are also being investigated for treating dyslipidaemia, inflammation, and insulin sensitivity, with promising effects in clinical trials.[59]
- **Stem Cell Therapy:** Stem cell therapy presents an innovative approach to regenerate damaged retinal tissue and slow disease progression.[60] Mesenchymal stem cells (MSCs) are particularly studied due to their anti-inflammatory properties and secretion of neuroprotective factors.[60] Adipose stem cells and bone marrow mesenchymal stem cells-derived exosomes show potential in mitigating retinal complications by suppressing pathways like Wnt/β-catenin, reducing oxidative stress, inflammation, and angiogenesis.[59] The mechanism involves enhancing microcirculation, stimulating new blood vessel growth, and delivering essential nutrients and oxygen to retinal tissues.[60] While promising for promoting accelerated tissue regeneration and protecting healthy cells, stem cell treatment currently cannot fully restore vision, and long-term safety and efficacy require extensive clinical trials.[61]
- **Nanotechnology:** Nanotechnology offers a transformative approach for drug delivery in DR, overcoming ocular barriers to precisely target the retina and minimize systemic side effects.[59]

Nanoparticles and nanocarriers improve bioavailability, enable sustained release of therapeutics, and offer potential for synergistic effects, leading to improved ocular bioavailability, prolonged therapeutic effects, and reduced dosing frequency.[59]

- **Gene Therapy:** Gene therapy holds immense potential for DR, aiming to achieve curative treatment by correcting pathogenic genes or altering the activity of existing abnormal genes.[29] Current strategies focus on inhibiting neovascularization and protecting neurovascular degeneration in the retina.[29] Preclinical studies using adeno-associated virus (AAV) mediated transduction to deliver anti-VEGF or other protective genes have shown promising results in animal models, offering advantages like longer therapeutic effects and reduced injection frequency.[29] However, safety, efficacy, and long-term effects need further validation through extensive clinical trials.[54]

B. Advanced Imaging and Artificial Intelligence (AI)

Advanced imaging modalities continue to evolve, providing invaluable new information for clinicians.[46] The integration of artificial intelligence (AI) with these imaging techniques is revolutionizing DR screening and monitoring.[62]

- **AI in Screening and Diagnosis:** AI algorithms, particularly deep learning and convolutional neural networks (CNNs), demonstrate remarkable accuracy in analysing retinal images, identifying early-stage DR with high sensitivity and specificity.[4] They address critical challenges such as intergrader variability in manual screening and the limited availability of specialists, especially in underserved regions.[62] AI-based grading systems can standardize diagnostics across different populations and provide rapid, automated diagnoses, prioritizing cases needing urgent attention.[63] This leads to significant cost savings by reducing workload on specialized personnel and optimizing resource allocation.[63]

- **Beyond Screening:** AI integration offers significant potential to address challenges in comprehensive diabetes care beyond just DR screening.[64] Retinal images analysed by AI can be used to diagnose other diabetes complications, including neuropathy, nephropathy, and atherosclerotic cardiovascular disease, and even predict the risk of future cardiovascular events.[64] This positions AI-assisted retinal image analysis as a potential central tool for modern personalized medicine in patients with diabetes.[64] The convergence of AI with telemedical systems allows for remote acquisition and automated analysis, enhancing speed and accuracy, and facilitating point-of-care screening even in resource-constrained settings.[62]

CONCLUSION

Diabetic retinopathy (DR) presents a significant global health challenge, causing preventable vision loss and substantial socioeconomic burden. Its complex pathogenesis, driven by hyperglycaemia, oxidative stress, and inflammation, highlights the need for holistic patient management. Early detection through regular eye exams and stringent control of blood glucose, blood pressure, and lipids are crucial. Current treatments like **laser photocoagulation**, **anti-VEGF injections**, and **vitrectomy** have improved outcomes. The future of DR management is bright, with emerging research in stem cell therapy, nanotechnology, gene therapy, and artificial intelligence promising more effective, personalized, and durable solutions to preserve vision and enhance the quality of life for millions worldwide.

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