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Review Article

Pathophysiology of Diabetic Retinopathy: A Brief Review

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Abstract

Diabetic retinopathy (DR) is a common and potentially blinding complication of diabetes mellitus, with a significant global impact on visual health. Uncontrolled diabetes can lead to many ocular disorders such as cataracts, glaucoma, ocular surface disorders, recurrent stye, non-arteritic anterior ischemic optic neuropathy, diabetic papillopathy, and DR. DR may lead to vision-threatening damage to the retina, eventually leading to blindness; it is the most common and severe ocular complication. Poor glycemic control, uncontrolled hypertension, dyslipidemia, nephropathy, male sex, and obesity are associated with worsening DR. Typical fundus features of DR include microaneurysms, hard exudates, macular edema (diabetic macular edema), and new vessels (in proliferative DR). The management options include strict control of the systemic conditions, intravitreal pharmacotherapy, and laser photocoagulation. With early diagnosis and prompt management, good final visual acuity may be achieved in most patients with DR. This review article aims to provide a comprehensive overview of pathophysiology DR.

Key words: Diabetes, Retinopathy, Inflammation

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia. One of the most devastating complications of diabetes is diabetic retinopathy (DR), a microvascular disease affecting the retina. DR is the leading cause of blindness among working-age adults worldwide, posing a significant public health burden. As the global prevalence of diabetes continues to rise, the importance of understanding DR's pathophysiology, clinical features, and management strategies becomes increasingly critical.

EPIDEMIOLOGY

DR stands out as the primary cause of vision impairment among individuals aged 20–74 years.[1] Between 1990 and 2010, DR held the fifth position in the list of the most common preventable causes of blindness and moderate-to-severe visual impairment.[2] Among diabetic patients, more than a third display signs of DR. Among these cases, a third suffers from vision-threatening DR, which includes severe non-proliferative DR, proliferative DR (PDR), or the presence of diabetic macular edema (DME).[3] These estimates are projected to escalate further due to the rising prevalence of diabetes, the aging of the population, and increased life expectancy among those with diabetes. PDR predominantly affects patients with Type 1 diabetes and constitutes the most common vision-threatening lesion. However, DME is responsible for the majority of vision loss in the highly prevalent Type 2 diabetes[4] and is consistently present in patients with Type 2 diabetes who also have PDR. Beyond vision loss, DR and DME have been implicated in the development of other diabetes-related complications, including nephropathy, peripheral neuropathy, and cardiovascular events. The most significant clinical risk factors for progressing to vision loss include the duration of diabetes, hyperglycemia, and hypertension. Effective control of serum glucose levels and blood pressure has demonstrated its efficacy in preventing vision loss stemming from DR. The prevalence and risk factors associated with DR have been extensively studied, encompassing regional

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and ethnic variations. However, there remains a relative scarcity of epidemiological data on DME. A review conducted in 2012 suggested that DME may afflict up to 7% of individuals with diabetes, with risk factors for DME largely mirroring those of DR. Recent publications have provided fresh insights into the epidemiology of both DR and DME, stemming from research conducted in both developed and developing countries.

PATHOPHYSIOLOGY

DR is a significant complication arising from DM, which remains a primary cause of vision loss among the working-age population. Diagnosis of DR is based on the clinical observation of vascular abnormalities within the retina. Clinically, DR is categorized into two distinct stages: Non-proliferative DR (NPDR) and PDR. NPDR represents the early phase of DR, characterized by increased vascular permeability and blockage of capillaries within the retinal vasculature. During this stage, retinal anomalies such as microaneurysms, hemorrhages, and hard exudates can be identified through fundus photography, even though patients may not exhibit symptoms. In contrast, PDR signifies a more advanced stage of DR, marked by the development of new blood vessels (neovascularization). At this stage, patients may experience severe vision impairment, particularly when these abnormal vessels bleed into the vitreous or when there is tractional retinal detachment. The primary cause of vision loss in DR patients is often DME, characterized by the swelling or thickening of the macula due to the accumulation of fluid within the macular region caused by the breakdown of the blood-retinal barrier (BRB).[5] DME can manifest at any stage of DR and results in distorted visual images and reduced visual acuity. The present treatment approaches for DR primarily focus on managing microvascular complications. These strategies encompass the use of intravitreal pharmacologic agents, laser photocoagulation, and vitreous surgery. Intravitreal administration of anti-vascular endothelial growth factor (anti-VEGF) agents presently constitutes the mainstay of therapy for both early and advanced DR stages. Unlike conventional laser therapy, which primarily stabilizes visual acuity, anti-VEGF therapy can lead to visual improvement while causing fewer ocular adverse effects. Consequently, studies investigating the underlying mechanisms of DR hold great significance as they may uncover potential targets for the development of alternative treatment approaches.

HYPERGLYCEMIA AND RETINAL MICROVASCULOPATHY

DR has long been acknowledged as a microvascular disorder, with hyperglycemia playing a pivotal role in the initiation of damage to retinal microvessels. Various metabolic pathways have been implicated in hyperglycemia-induced vascular injury, including the polyol pathway, the accumulation of advanced glycation end products (AGEs), activation of the protein kinase C (PKC) pathway, and engagement of the hexosamine pathway.[6-10] In the polyol pathway, excess glucose is metabolized through the polyol pathway to sorbitol. Sorbitol is impermeable to cellular membranes, accumulating inside the cell and inducing osmotic damage. It can also be metabolized to fructose and subsequently to fructose-3-phosphate and deoxyglucosone, both of which are strong glycolyzing agents and lead to the deposition of AGEs. In addition, upregulation of the polyol pathway results in a reduced availability of nicotinamide adenine dinucleotide phosphate (NADPH), thereby enhancing the sensitivity of affected cells to oxidative stress. Due to the high availability of glucose, AGEs formation is markedly increased in diabetic patients. AGEs have the capacity to cross-link proteins which alters their structure and function, affecting basement membranes, cellular receptors, and blood vessel wall components. Moreover, AGEs receptor activation induces pro-oxidant and pro-inflammatory cascades, thus exacerbating oxidative stress and leukocyte adhesion. The accumulation of AGEs has also been correlated to pericyte loss. An increase in glycolysis activity also occurs during hyperglycemic episodes, elevating the synthesis of diacylglycerol which in turn activates the PKC pathway. PKC activates the mitogen-activated protein kinase factors, leading to enhanced expression of stress-related proteins and mediators of vascular function such as c-Jun kinases and heat shock proteins. In particular, the PKC-β isoform increases VEGF expression. PKC activation also drives over-expression of NADPH oxidase and NFκB in vascular cells, exacerbating oxidative stress, and inflammation. In response to hyperglycemia, the initial reactions of retinal blood vessels include vessel dilation and alterations in blood flow. These responses are believed to be part of metabolic autoregulation mechanisms designed to enhance retinal metabolism in individuals with diabetes. Another prominent feature of the early stages of DR is the loss of pericytes. Both *in vitro* and *in vivo* studies have demonstrated evidence of pericyte apoptosis triggered by elevated glucose levels.[5,6] Given that pericytes provide crucial structural support to capillaries, their loss results in localized protrusions in capillary walls, a process associated with the formation of microaneurysms, which represent the earliest clinical indication of DR. Furthermore, alongside pericyte loss, apoptosis of endothelial cells and thickening of the basement membrane are also observed during the development of DR. These factors collectively contribute to the impairment of the BRB. In addition, substantial pericyte and endothelial cell loss leads to capillary occlusion and ischemia. Retinal ischemia/hypoxia prompts the upregulation of vascular endothelial growth

factor (VEGF) by activating hypoxia-inducible Factor 1 (HIF-1). Another line of evidence suggests that the diabetic condition's elevation of phospholipase A2 also triggers VEGF upregulation VEGF, a pivotal player in the progression of PDR and DME, is thought to increase vascular permeability by inducing the phosphorylation of tight junction proteins such as occludin and zonula occludens-1.[11] In addition, as an angiogenic factor, VEGF stimulates endothelial cell proliferation through the activation of mitogen-activated protein pathways. Elevated VEGF expression has been identified in the retinas of diabetic mice, as well as in the vitreous of patients with DME and PDR Beyond VEGF, other angiogenic factors, such as angiopoietins (Ang-1, Ang-2), also play a role in modulating vascular permeability through interaction with endothelial receptor tyrosine kinase Tie-2. Notably, Ang-2, an antagonist of Tie2, has been shown to promote vascular leakage in the retinas of diabetic rats. Speculation arises that angiogenic factors aside from VEGF may contribute to alterations in the microvasculature during DR, potentially offering novel targets for therapeutic intervention.

CLASSIFICATION

Early treatment DR study (ETDRS) classification.

NPDR

- No retinopathy: No retinal lesions
- Very mild NPDR: Microaneurysms only
- Mild NPDR: A few microaneurysms, retinal hemorrhages and hard exudates
- Moderate NPDR: Retinal hemorrhages (about 20 medium-large per quadrant) in 1–3 quadrants + cotton wool spots (between the grades mild and severe NPDR)
- Severe NPDR: fulfilling one rule of the 4-2-1 rule.
    - Severe hemorrhages in all four quadrants
    - Venous beading in two or more quadrants
    - Moderate IRMA in one or more quadrants.

Very severe NPDR: fulfilling two or more rules of the 4-2-1 rule.

PDR

- Mild-to-moderate PDR-NVD or NVE insufficient to meet high-risk characteristics
- High-risk PDR
- NVD greater than ETDRS standard photograph 10A (about 1/3 disk area).
- Any NVD with vitreous hemorrhage.
- NVE >1/2 disc area with vitreous hemorrhage.

Advanced diabetic eye disease is the end-stage vision-threatening complication of DR in patients whose treatment is inadequate or unsuccessful. It may present as pre-retinal or intragel hemorrhage, tractional retinal detachment, or rubeosis iridis.

DME can be classified into the following groups:

- Focal exudative and diffuse maculopathy
- Ischemic and non-ischemic maculopathy
- Tractional and non-tractional maculopathy
- Center involving macular edema and non-center involving macular edema.

ETDRS definition of clinically significant macular edema (CSME):

- Retinal edema within 500 μm of the center of the fovea
- Hard exudates within 500 μm of the center of the fovea if associated with adjacent retinal thickening (which may be outside the 500 μm limit)
- Retinal edema one disk area (1500 μm) or larger, any part of which is within one disc diameter of the center of the fovea.

Optical coherence tomography classification of DME:

- Sponge-like thickening of retinal layers
- Large cystoid spaces
- Serous detachment of the retina
- Tractional detachment of the fovea or vitreomacular traction
- Taut posterior hyaloid membrane.

International clinical DR disease severity scale:

- No apparent retinopathy – No abnormality
- Mild NPDR – Microaneurysms only
- Moderate NPDR – More than just microaneurysms and less than severe disease
- Severe NPDR – No signs of PDR and any of the following:
    - 20 intraretinal hemorrhages in each of the four quadrants
    - Venous beading in ≥2 quadrants
    - Prominent IRMA ≥1 quadrant
- PDR – One or more of the following:
    - Neovascularization
    - Vitreous or pre-retinal hemorrhage

With regards to DME, the DME may be:

- "DME apparently absent" – Apparent retinal thickening and hard exudates at the posterior pole are absent.
- "DME apparently present" – There is some "apparent retinal thickening and hard exudates at the posterior

pole." It can further be classified into mild, moderate, and severe based on the distance of thickening and hard exudates from the center of the fovea.

- Mild DME: The retinal thickening or hard exudates are located far from the center of the fovea.
- Moderate DME: Retinal thickening or hard exudates are approaching the center of the macula but not involving the center
- Severe DME: Hard exudate and thickening involve the center of the fovea.

INFLAMMATION

Inflammation plays a crucial role in the development of DR. Chronic, low-grade inflammation has been consistently observed in various stages of DR, both in diabetic animal models and in patients.[12-16] In the early stages of DR, leukostasis, characterized by the adherence of monocytes and granulocytes to retinal microvasculature, is a recognized critical process. This phenomenon was first reported by Schröder *et al.* in 1991 when they observed the occlusion of retinal microvessels by monocytes and granulocytes in diabetic rats induced by streptozotocin. Increased adherence of leukocytes to retinal blood vessels was detected as early as 3 days after the onset of diabetes in rats.[17] Notably, this increased leukostasis was found to be spatially associated with endothelial damage and impairment of the BRB in diabetic rats. Subsequent studies further elucidated that leukostasis contributed to the loss of endothelial cells and the breakdown of the BRB, primarily through the Fas (CD95)/Fas-ligand pathway.[18] The adhesion of leukocytes to endothelial cells, a key element in leukostasis, is mediated by adhesion molecules. Diabetic rats and patients have been reported to exhibit increased leukocyte adhesion, along with upregulated expression of leukocyte b2-integrins CD11a, CD11b, and CD18.[19,20] In addiion, levels of endothelial cell adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule (VCAM)-1, and selectins (E-selectin) have been found to be elevated in diabetic animals and patients. Notably, the expression of VCAM-1 and E-selectin in patients' plasma correlates with the severity of DR genetic deficiencies in CD18 or ICAM-1 have resulted in a significant reduction in adherent leukocytes. Inhibition of CD18 or ICAM-1 using anti-CD18 F(ab9)2 fragments or antibodies has been shown to decrease retinal leukostasis and vascular abnormalities in diabetic rats. Chemokines, which regulate the recruitment and activation of leukocytes, have also been implicated in the pathogenesis of DR. In diabetic patients, chemokines such as monocyte chemotactic protein-1 (MCP-1), macrophage inflammatory protein-1alpha (MIP-1α), and MIP-1β have been reported to be elevated. Deficiency in MCP-1 has led to reduced retinal vascular leakage in diabetic mice. In addition, inflammatory cytokines including tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), IL-8, and IL-1β have been significantly upregulated in diabetic patients, and their expression levels are correlated with the severity of DR. Chemokines, which regulate the recruitment and activation of leukocytes, have also been implicated in the pathogenesis of DR. In diabetic patients, chemokines such as MCP-1, MIP-1α, and MIP-1β have been reported to be elevated. Deficiency in MCP-1 has led to reduced retinal vascular leakage in diabetic mice. In addition, inflammatory cytokines including TNF-α, IL-6, IL-8, and IL-1β have been significantly upregulated in diabetic patients, and their expression levels are correlated with the severity of DR.

RETINAL NEURODEGENERATION

Retinal neurodegeneration represents one of the initial events in the progression of DR. In diabetic rats, the apoptosis of retinal neurons becomes evident as early as 1 month after the onset of diabetes.[21] Notably, an upregulation of pro-apoptotic molecules such as cleaved caspase-3, Bax, and Fas has been observed in retinal neurons in both diabetic animals and individuals with diabetes.[22-24] Mitochondrial dysfunction has also been implicated in the degeneration of the retina in DR. In the retinas of diabetic subjects, there is a notable increase in the expression of pro-apoptotic mitochondrial proteins like cytochrome c and apoptosis-inducing factor. *In vitro* studies have further demonstrated that exposure to high glucose levels is linked to heightened mitochondrial fragmentation and cellular apoptosis In addition to mitochondrial damage, researchers have extensively investigated the involvement of oxidative stress in diabetes-induced retinal degeneration. In diabetic mouse retinas, there is a significant increase in the generation of reactive oxygen species (ROS). Suppressing ROS generation has proven effective in preventing visual impairment and caspase-3-mediated apoptosis of retinal neurons. Notably, mounting evidence suggests that retinal neurodegeneration may represent an independent pathophysiological process in DR. In a mouse model of diabetes, the loss of ganglion cells and a reduction in retinal thickness were observed before the onset of microvascular changes.[25-27] Similarly, in diabetic patients, inner retinal thinning has been detected in the absence of DR or with minimal DR (microaneurysms). Therefore, further exploration of the molecular mechanisms underpinning retinal neurodegeneration may yield promising therapeutic targets for early intervention in DR.

CONCLUSION

The pathophysiology of DR is fascinating and complex, with many mechanisms that need further study. DR

treatment is an economic burden due to the number of patients affected and the cost of anti-VEGF therapies. Therefore, filling the gaps in the landscape of DR pathophysiology is of the utmost importance for a better understanding of the disease.

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