

# Exploring the Mechanisms Linking Hyperglycemia-Induced Retinal Microvascular Injury to Diabetic Complications

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**Abstract: Background/Aim:** Diabetic microvascular complications represent the leading causes of morbidity and mortality in patients with diabetes mellitus. Diabetic retinopathy (DR), as the most representative target-organ manifestation, demonstrates significant clinical comorbidity with systemic complications including nephropathy, neuropathy, foot disease, and cardiovascular events; however, the underlying integrative mechanisms remain inadequately systematized. This review aims to delineate the molecular and cellular mechanisms of hyperglycemia-induced retinal microvascular injury, explore the structural homology, shared pathways, and systemic bridge mediators linking this injury to major diabetic complications, and provide a theoretical basis for complication prevention and control from a “retina-systemic” network perspective. **Methods:** A systematic literature search was conducted across PubMed, Web of Science, Cochrane Library, and Embase for original research articles, systematic reviews, and meta-analyses published between 2010 and 2026. Search terms included “diabetic retinopathy,” “microvascular injury,” “diabetic complications,” “hyperglycemia,” “systemic inflammation,” and “metabolic memory.” A mechanistic integration analysis was performed on included studies. **Results:** Hyperglycemia induces retinal microvascular injury through activation of the polyol pathway, the advanced glycation end products (AGEs)-RAGE axis, protein kinase C (PKC)- $\beta$  activation, oxidative stress, and NLRP3 inflammasome-mediated chronic inflammation, culminating in pericyte loss, blood-retinal barrier (BRB) disruption, and increased microvascular permeability. Retinal microvasculature exhibits high structural homology with glomerular, nerve endoneurial, and lower-extremity microvessels in basement membrane composition, pericyte coverage, and molecular pathways. Systemic low-grade inflammation, circulating endothelial progenitor cell (EPC) depletion, renin-angiotensin-aldosterone system (RAAS) activation, metabolic memory, epigenetic modifications, and gut microbiota dysbiosis serve as critical bridge mediators through which retinal injury mediates or predicts systemic multi-organ complications. Furthermore, retinal vascular parameters and DR staging demonstrate independent predictive value for systemic complication risk. **Conclusions:** Retinal microvascular injury is not merely an ocular complication of diabetes but constitutes an integral component of systemic microvascular disease and a “visual window” thereof. Early intervention targeting the shared molecular pathways and systemic mediators of hyperglycemia-induced microvascular injury holds significant clinical importance for the integrated prevention and management of diabetic multi-organ complications.

**Keywords:** Diabetes Mellitus; Diabetic Retinopathy; Microvascular Injury; Diabetic Complications; Pathogenesis

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## 1. Introduction

Diabetes mellitus has emerged as one of the most severe public health challenges of the 21st century. According to the International Diabetes Federation (IDF), the global population of adults aged 20-79 years with diabetes has reached 589 million, with prevalence continuing to rise <sup>[1]</sup>. Diabetic microvascular complications--including retinopathy, nephropathy, and neuropathy--represent the characteristic chronic target-organ damage of diabetes and constitute the predominant sources of disability, mortality, and healthcare burden <sup>[2]</sup>. The microvascular system, as the primary target of hyperglycemic injury, undergoes pathological alterations that permeate the entire course of diabetic complication development; thus, elucidating the mechanisms of microvascular injury is central to complication prevention and control.

Diabetic retinopathy (DR) is one of the most common and representative microvascular complications of diabetes, affecting approximately one-third of the diabetic population and serving as the leading cause of irreversible blindness among working-age adults <sup>[2,3]</sup>. Pathologically, DR is characterized by retinal capillary pericyte loss, basement membrane thickening, blood-retinal barrier (BRB) disruption, and microaneurysm formation, collectively embodying the classical pathological process of hyperglycemia-induced microvascular injury <sup>[2,4]</sup>. Given that retinal microvasculature possesses typical structural and functional features of the systemic microvascular system, DR has long been regarded as an ideal model for investigating the pathological mechanisms of diabetic microangiopathy.

In recent years, evolving understanding of diabetic complications has transformed the clinical positioning of DR from a purely ocular complication to a “visual window” for systemic microvascular disease. Extensive epidemiological studies have demonstrated that the presence and severity of DR are significantly associated with the risks of diabetic kidney disease, cardiovascular events, peripheral neuropathy, and foot ulcers, suggesting that retinal microvascular injury and systemic multi-organ complications may share a common molecular soil <sup>[5]</sup>. As the only microvascular bed directly observable in vivo through non-invasive means, the retina provides a unique avenue for assessing systemic microcirculatory status through its vascular morphological and functional parameters. However, existing research has predominantly focused on the local pathology of DR or the independent mechanisms of single complications. A systematic mechanistic integration and theoretical framework remain lacking regarding how hyperglycemia-induced retinal microvascular injury mediates or predicts systemic multi-organ complications through systemic low-grade inflammation, circulating endothelial progenitor cell depletion, renin-angiotensin-aldosterone system activation, metabolic memory effects, and gut microbiota dysbiosis.

Accordingly, this review systematically summarizes the molecular and cellular mechanisms of hyperglycemia-induced retinal microvascular injury, deeply explores the structural homology, shared pathways, and systemic bridge mechanisms between this injury and major diabetic complications (renal, neural, cardiovascular, and foot disease), and proposes clinical risk stratification and intervention strategies from a “retina-systemic” microvascular network perspective, providing a theoretical foundation for the integrated prevention and management of diabetic complications.

## 2. Molecular and Cellular Mechanisms of Hyperglycemia-Induced Retinal Microvascular Injury

Chronic hyperglycemia systematically disrupts the structural and functional integrity of retinal microvasculature through metabolic stress, oxidative damage, chronic inflammation, and hemodynamic disturbances. These mechanisms do not operate in isolation but form a positive-feedback network through key nodes including reactive oxygen species (ROS), nuclear factor-kappa B (NF-κB), and vascular endothelial growth factor (VEGF), collectively driving the initiation and progression of retinal microvascular injury <sup>[8]</sup>.

### 2.1 Metabolic Stress-Activated Signaling Pathways

#### 2.1.1 Polyol Pathway Activation: Aldose Reductase, Sorbitol Accumulation, and Osmotic-Oxidative Dual Stress

Under hyperglycemic conditions, aldose reductase (AR) reduces glucose to sorbitol, which is subsequently oxidized to fructose by sorbitol dehydrogenase. Sorbitol, as a polar polyol with limited membrane permeability, accumulates within retinal pericytes and endothelial cells, elevating osmotic pressure and triggering cellular edema and ionic dyshomeostasis. Concurrently, AR competitively consumes reduced nicotinamide adenine dinucleotide phosphate (NADPH), impairing

glutathione (GSH) regeneration and diminishing cellular antioxidant capacity; the sorbitol dehydrogenase oxidation reaction increases the NADH/NAD<sup>+</sup> ratio, exacerbating mitochondrial oxidative pressure. Pericytes exhibit particular sensitivity to polyol pathway activation, and this pathway represents an important mechanism for early pericyte loss in the retina<sup>[8]</sup>.

### **2.1.2 Advanced Glycation End Products (AGEs)-RAGE Axis: Basement Membrane Deposition and NF-κB Inflammatory Cascade**

AGEs are generated at an accelerated rate through non-enzymatic glycation reactions and damage microvasculature through two principal pathways: first, AGEs covalently cross-link type IV collagen and laminin, directly causing capillary basement membrane thickening and increased permeability<sup>[26]</sup>; second, AGEs bind to their receptor RAGE, activating NADPH oxidase, inducing ROS burst, and subsequently activating NF-κB to upregulate the transcription of pro-inflammatory genes including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interleukin-1β (IL-1β), and vascular endothelial growth factor (VEGF)<sup>[28]</sup>. RAGE itself is also an NF-κB target gene, forming an “AGEs-RAGE-ROS-NF-κB” positive-feedback amplification loop.

### **2.1.3 Protein Kinase C (PKC)-β Activation: Diacylglycerol Accumulation and Vascular Endothelial Growth Factor Overexpression**

Hyperglycemia increases diacylglycerol (DAG) synthesis, preferentially activating the PKC-β isoform<sup>[9,11]</sup>. PKC-β promotes VEGF gene transcription and secretion through downstream transcriptional signaling, significantly increasing vascular permeability<sup>[10]</sup>; it also inhibits endothelial nitric oxide synthase (eNOS) activity, promotes endothelin-1 (ET-1) expression, and causes vasomotor dysfunction. Furthermore, PKC-β can phosphorylate tight junction proteins, directly disrupting intercellular junctional integrity.

### **2.1.4 Hexosamine Pathway Activation: Aberrant Glycosylation and Transcription Factor Dysfunction**

Approximately 2%-5% of glucose enters the hexosamine biosynthesis pathway, where glutamine:fructose-6-phosphate amidotransferase (GFAT) catalyzes the generation of uridine diphosphate N-acetylglucosamine (UDP-GlcNAc). Elevated UDP-GlcNAc levels cause aberrant O-linked N-acetylglucosamine (O-GlcNAc) modification of key transcription factors including Sp1 and NF-κB, enhancing the transcription of genes such as transforming growth factor-beta 1 (TGF-β1), plasminogen activator inhibitor-1 (PAI-1), and VEGF<sup>[12]</sup>. This pathway exhibits metabolic cross-talk with the polyol pathway, AGEs formation, and PKC activation, collectively constituting the metabolic stress network<sup>[8]</sup>.

## **2.2 Oxidative Stress and Mitochondrial Injury**

The mitochondrial electron transport chain (ETC) becomes overloaded with electron donors under hyperglycemic conditions, with electron leakage increasing exponentially at complexes I and III, generating superoxide anion (O<sub>2</sub><sup>•-</sup>) that is subsequently converted to highly reactive hydroxyl radicals (•OH) through dismutation and Fenton reactions<sup>[13]</sup>. Mitochondrial DNA (mtDNA) lacks histone protection and possesses limited repair capacity, rendering it exquisitely sensitive to ROS; mtDNA damage impairs the synthesis of core respiratory chain subunits, leading to energy metabolic failure<sup>[14]</sup>.

Concurrently, antioxidant defense systems become progressively depleted: the polyol pathway competitively consumes NADPH, weakening GSH regeneration; chronic hyperglycemia suppresses the expression of manganese superoxide dismutase (SOD2), catalase (CAT), and glutathione peroxidase (GPx) through epigenetic modifications<sup>[15]</sup>. The decompensation of antioxidant systems marks the transition of retinal microvascular endothelial cells into a state of sustained oxidative damage.

## **2.3 Inflammatory Response and Immune Regulation**

### **2.3.1 NLRP3 Inflammasome Activation and IL-1β/IL-18 Maturation and Release**

Hyperglycemia activates the NLRP3 inflammasome through a “two-signal” mechanism: the NF-κB pathway provides the priming signal, promoting NLRP3 and pro-IL-1β expression; mitochondrial ROS induce oxidation of thioredoxin (Trx), causing its dissociation from thioredoxin-interacting protein (TXNIP), and the liberated TXNIP binds to and activates NLRP3, providing the activation signal<sup>[16,29]</sup>. Activated caspase-1 cleaves pro-IL-1β and pro-IL-18 into their mature forms and induces pyroptosis, releasing inflammatory contents and amplifying local inflammatory responses<sup>[17]</sup>.

### **2.3.2 NF-κB Cascade Amplification and Pro-inflammatory Gene Transcription**

NF- $\kappa$ B serves as the central transcription factor regulating inflammation. Hyperglycemia activates I $\kappa$ B kinase (IKK) through the AGEs-RAGE, PKC- $\beta$ , and ROS pathways, leading to I $\kappa$ B degradation and nuclear translocation of the NF- $\kappa$ B p65 subunit, which initiates the transcription of pro-inflammatory genes including intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), TNF- $\alpha$ , IL-6, and monocyte chemoattractant protein-1 (MCP-1), promoting leukocyte adhesion to and transendothelial migration across endothelial cells <sup>[18]</sup>.

### 2.3.3 Macrophage Infiltration and Microglial Activation

Retinal microglia become activated under hyperglycemic stimulation and release inflammatory mediators. Concurrently, adhesion molecules and MCP-1 expressed by endothelial cells recruit circulating monocytes that infiltrate retinal tissue and differentiate into pro-inflammatory M1 macrophages. Microglia and M1 macrophages form an “inflammatory symbiosis,” maintaining a chronic inflammatory microenvironment in the retina that drives pericyte apoptosis, basement membrane remodeling, and neovascularization <sup>[18]</sup>.

## 2.4 Hemodynamic Alterations and Blood-Retinal Barrier Disruption

### 2.4.1 Nitric Oxide/Endothelin-1 Imbalance and Vasomotor Dysfunction

PKC- $\beta$  activation and excessive ROS generation inhibit eNOS activity and promote the reaction of NO with superoxide anion to form peroxynitrite (ONOO<sup>-</sup>), resulting in significantly decreased NO bioavailability <sup>[8,19]</sup>; concurrently, ET-1 expression is upregulated, mediating vasoconstriction through the type A receptor (ETA). NO/ET-1 imbalance disrupts retinal blood flow autoregulation, exacerbating tissue ischemia and hypoxia, and establishing a vicious cycle of “ischemia-VEGF release-increased permeability.”

### 2.4.2 Tight Junction Protein Downregulation and Intercellular Junction Dissociation

Tight junctions between retinal capillary endothelial cells are composed of transmembrane proteins occludin and claudin-5, and cytoplasmic scaffold protein zonula occludens-1 (ZO-1). Hyperglycemia causes tight junction dissociation and widened intercellular gaps through PKC- $\beta$ -mediated direct phosphorylation of junctional proteins, VEGF-induced occludin endocytosis and degradation, ROS-mediated oxidation of protein sulfhydryl groups, and inflammatory factor-induced activation of myosin light chain kinase (MLCK), thereby increasing BRB permeability <sup>[20]</sup>.

### 2.4.3 Pericyte Apoptosis and Destruction of the Endothelial Cell-Pericyte-Basement Membrane Unit

Pericytes are critical cells for maintaining capillary stability, and their survival depends on the binding signal of platelet-derived growth factor-BB (PDGF-BB) secreted by endothelial cells to PDGF receptor- $\beta$  (PDGFR- $\beta$ ) on the pericyte surface <sup>[21]</sup>. Polyol pathway injury, AGEs toxicity, and reduced PDGF-BB secretion from endothelial cells collectively induce pericyte apoptosis and detachment <sup>[22]</sup>. Following pericyte loss, endothelial cells lose growth-inhibitory signals, proliferate uncontrollably to form microaneurysms, and exposed basement membrane areas increase, permitting plasma component extravasation.

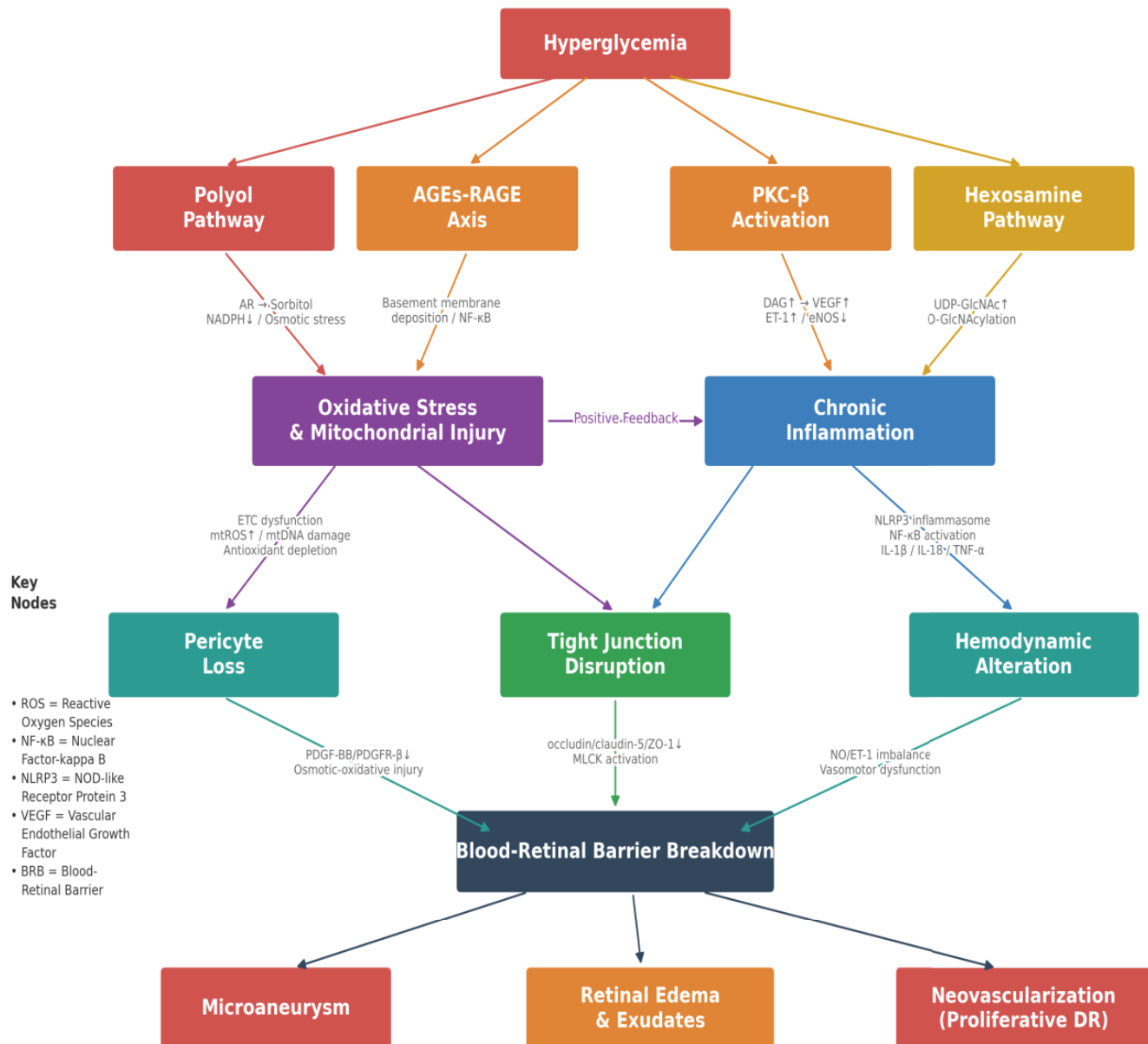
### 2.4.4 Blood-Retinal Barrier Disruption, Microaneurysm Formation, and Increased Vascular Permeability

The integrated effects of the aforementioned mechanisms manifest as functional BRB disruption: tight junction dissociation and pericyte loss lead to plasma protein and fluid leakage, forming retinal edema and hard exudates; microaneurysms have thin, fragile walls that readily rupture, becoming the source of dot hemorrhages; capillary occlusion creates retinal non-perfusion areas, stabilizing hypoxia-inducible factor-1 $\alpha$  (HIF-1 $\alpha$ ) and driving massive VEGF expression that initiates pathological neovascularization, marking the progression of DR from the non-proliferative to the proliferative stage <sup>[2,23]</sup>.

Chronic hyperglycemia activates four metabolic stress pathways (the polyol pathway, the AGEs-RAGE axis, PKC- $\beta$  activation, and the hexosamine pathway), which converge on oxidative stress with mitochondrial injury and chronic inflammation; the two hubs amplify each other through a positive feedback loop. These mechanisms drive pericyte loss, tight junction disruption, and hemodynamic alteration, culminating in blood-retinal barrier (BRB) breakdown and the characteristic lesions of diabetic retinopathy, including microaneurysm, retinal edema and exudates, and neovascularization in proliferative diabetic retinopathy. AR, aldose reductase; AGEs, advanced glycation end products; RAGE, receptor for AGEs; DAG, diacylglycerol; VEGF, vascular endothelial growth factor; UDP-GlcNAc, uridine diphosphate N-acetylglucosamine; ETC, electron transport chain; mtROS, mitochondrial reactive oxygen species; mtDNA, mitochondrial DNA; NLRP3, NOD-like

receptor protein 3; NF- $\kappa$ B, nuclear factor-kappa B; IL, interleukin; TNF- $\alpha$ , tumor necrosis factor-alpha; ET-1, endothelin-1; eNOS, endothelial nitric oxide synthase; MLCK, myosin light chain kinase; PDGF-BB, platelet-derived growth factor-BB; PDGFR- $\beta$ , platelet-derived growth factor receptor- $\beta$ ; NO, nitric oxide; BRB, blood-retinal barrier.

Figure 1: Molecular Network of Hyperglycemia-Induced Retinal Microvascular Injury



### 3. Structural Homology between Retinal Microvasculature and Systemic Target-Organ Microvessels

That retinal microvascular injury can serve as a “visual window” for systemic microvascular disease stems fundamentally from the high degree of structural homology between retinal microvasculature and glomerular, nerve endoneurial, and lower-extremity microvessels in tissue architecture, cellular composition, and functional characteristics. This structural homology provides a unified anatomical foundation for understanding hyperglycemia-induced multi-organ microvascular injury.

#### 3.1 Common Features of Basement Membrane Structure

Retinal capillaries, glomerular capillary loops, and nerve endoneurial microvessels all possess continuous basement membranes that serve as structural scaffolds between endothelial cells and surrounding tissues. Basement membranes are primarily composed of type IV collagen, laminin, nidogen, and heparan sulfate proteoglycans. In the hyperglycemic microenvironment, covalent cross-linking of basement membrane proteins by AGEs, PKC- $\beta$  activation-induced TGF- $\beta$ 1 overexpression promoting

excessive collagen synthesis, and matrix metalloproteinase (MMP)/tissue inhibitor of metalloproteinase (TIMP) imbalance-mediated remodeling abnormalities all manifest as progressive basement membrane thickening across the microvasculature of these organs <sup>[26]</sup>. Glomerular basement membrane thickening is an early pathological hallmark of diabetic kidney disease (DKD), while nerve endoneurial microvascular basement membrane thickening is closely associated with nerve fiber ischemia and axonal degeneration <sup>[25]</sup>. Thus, retinal capillary basement membrane thickening is not only a histological feature of DR but also reflects the common pathological process of systemic microvascular basement membrane disease.

### 3.2 Pericyte Coverage and Vascular Stability Regulation

Pericytes (or functionally analogous vascular smooth muscle-like cells) are critical cellular components for maintaining microvascular stability. Retinal capillary pericytes exhibit a pericyte-to-endothelial cell ratio as high as 1:1; glomerular mesangial cells and nerve endoneurial capillary pericytes share high functional similarity with retinal pericytes, all regulating endothelial cell survival, proliferation, and barrier function through the PDGF-BB/PDGFR- $\beta$ , angiopoietin-1 (Ang-1)/Tie-2, and TGF- $\beta$ /Alk5/Smad signaling axes <sup>[21,22]</sup>. Hyperglycemia-induced pericyte loss or functional abnormalities manifest as capillary acellularity and microaneurysm formation in the retina, mesangial cell detachment and glomerular sclerosis in the kidney, and blood-nerve barrier disruption and nerve endoneurial edema in peripheral nerves. The commonality of cross-organ pericyte injury suggests that therapeutic strategies targeting pericyte protection may confer systemic microvascular benefits.

### 3.3 Endothelial Cell Phenotype and Barrier Function

The endothelial cells (or epithelial cells) of the retina, glomerulus, and blood-nerve barrier all exhibit phenotypic characteristics of high tight junction protein expression, forming the BRB, glomerular filtration barrier, and blood-nerve barrier, respectively, which strictly restrict the free passage of plasma proteins and inflammatory cells. The mechanisms by which hyperglycemia disrupts these barriers are highly consistent: all involve downregulation of junctional proteins such as occludin and claudin-5 (or glomerular podocyte nephrin and podocin) and increased permeability induced by inflammatory mediators including VEGF and TNF- $\alpha$  <sup>[20,25]</sup>. This cross-organ homology of barrier function further supports the theoretical positioning of DR as an indicator of systemic microvascular barrier disease.

*Table 1. Structural Homology Between Retinal Microvasculature and Systemic Target Organs*

| Comparison Dimension                  | Retina                                                                                                    | Glomerulus                                                                                                             | Nerve Endoneurium                                                                                         | Lower Extremity/ Foot                                                                                     |
|---------------------------------------|-----------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------|
| <b>Basement Membrane Components</b>   | Type IV collagen, laminin, nidogen, heparan sulfate proteoglycans                                         | Type IV collagen, laminin, nidogen, heparan sulfate proteoglycans                                                      | Type IV collagen, laminin, nidogen, heparan sulfate proteoglycans                                         | Type IV collagen, laminin, nidogen, heparan sulfate proteoglycans                                         |
| <b>Pericytes/ Mesangial Cells</b>     | Pericytes (pericyte: endothelial ratio $\approx$ 1:1)                                                     | Mesangial cells (functionally pericyte-like)                                                                           | Capillary pericytes (lower coverage density)                                                              | Capillary pericytes (lower coverage density)                                                              |
| <b>Barrier Type</b>                   | Blood-retinal barrier (BRB)                                                                               | Glomerular filtration barrier (GFB)                                                                                    | Blood-nerve barrier (BNB)                                                                                 | Skin microcirculation barrier                                                                             |
| <b>TJ/SD Proteins</b>                 | occludin, claudin-5, ZO-1                                                                                 | nephrin, podocin, ZO-1 (podocytes)                                                                                     | occludin, claudin-5, ZO-1                                                                                 | occludin, claudin-5, ZO-1                                                                                 |
| <b>Main Injury Manifestations</b>     | Pericyte loss, basement membrane thickening, BRB breakdown, microaneurysms, neovascularization            | Mesangial cell detachment, basement membrane thickening, podocyte foot-process fusion, proteinuria, glomerulosclerosis | Pericyte loss, basement membrane thickening, BNB disruption, endoneurial edema, axonal degeneration       | Pericyte loss, basement membrane thickening, vascular occlusion, tissue ischemia, ulcer formation         |
| <b>Shared Core Signaling Pathways</b> | Polyol pathway, AGEs-RAGE, PKC- $\beta$ /VEGF, hexosamine pathway, oxidative stress, NLRP3/NF- $\kappa$ B | Polyol pathway, AGEs-RAGE, PKC- $\beta$ /VEGF, hexosamine pathway, oxidative stress, NLRP3/NF- $\kappa$ B              | Polyol pathway, AGEs-RAGE, PKC- $\beta$ /VEGF, hexosamine pathway, oxidative stress, NLRP3/NF- $\kappa$ B | Polyol pathway, AGEs-RAGE, PKC- $\beta$ /VEGF, hexosamine pathway, oxidative stress, NLRP3/NF- $\kappa$ B |
| <b>Common Pathological Outcome</b>    | Increased microvascular permeability, tissue ischemia-hypoxia, fibrotic remodeling                        | Increased microvascular permeability, tissue ischemia-hypoxia, fibrotic remodeling                                     | Increased microvascular permeability, tissue ischemia-hypoxia, fibrotic remodeling                        | Increased microvascular permeability, tissue ischemia-hypoxia, fibrotic remodeling                        |

The table compares retinal, glomerular, nerve endoneurial, and lower-extremity microvessels across seven dimensions: basement membrane components, pericytes/mesangial cells, barrier type, tight junction/slit diaphragm proteins, main injury manifestations under hyperglycemia, shared core signaling pathways, and common pathological outcomes. BRB, blood-retinal barrier; GFB, glomerular filtration barrier; BNB, blood-nerve barrier; TJ, tight junction; SD, slit diaphragm.

## 4. Shared Molecular Pathways: The “Common Soil” from Retina to Systemic Complications

Retinal microvascular injury and diabetic systemic complications are not isolated pathological events but rather represent systemic manifestations of the same molecular pathways operating in different target organs. Hyperglycemia-induced metabolic stress, oxidative damage, and inflammatory signals activate highly conserved molecular cascades in retinal, renal, neural, cardiovascular, and lower-extremity microvasculature, constituting the “common soil” for multi-organ complication development.

### 4.1 Systemic Effects of the Polyol Pathway and AGEs-RAGE Axis

Polyol pathway activation and AGEs-RAGE axis activation are not confined to the retina but have also been demonstrated in glomerular mesangial cells, nerve endoneurial Schwann cells, and cardiac microvascular endothelial cells. Glomerular mesangial cells highly express AR, and sorbitol accumulation directly promotes mesangial cell apoptosis and excessive extracellular matrix deposition; AGEs deposition in the glomerular basement membrane and mesangium is a key driver of DKD progression<sup>[8,26]</sup>. In peripheral nerve tissue, polyol pathway activation causes Schwann cell dysfunction and axonal transport impairment, while the AGEs-RAGE axis promotes nerve endoneurial inflammation and neurodegeneration<sup>[24]</sup>. Thus, the polyol pathway and AGEs-RAGE axis constitute the core metabolic pathways linking retinal and systemic microvascular injury.

### 4.2 Cross-Organ Activation of the PKC- $\beta$ /VEGF Pathway

PKC- $\beta$  activation and its downstream VEGF overexpression represent the core mechanisms of increased vascular permeability and neovascularization in DR. The same pathway promotes upregulated glomerular VEGF expression and disrupts the glomerular filtration barrier in DKD; induces increased myocardial microvascular permeability and interstitial fibrosis in diabetic cardiomyopathy; and promotes aberrant wound neovascularization and increased permeability in diabetic foot disease, exacerbating tissue edema and healing impairment<sup>[10]</sup>. The protective effects of the PKC- $\beta$  inhibitor ruboxistaurin in DR clinical trials<sup>[27]</sup>, and the widespread application of anti-VEGF therapy in diabetic macular edema and proliferative DR, both suggest that targeting this pathway may confer cross-organ microvascular protection.

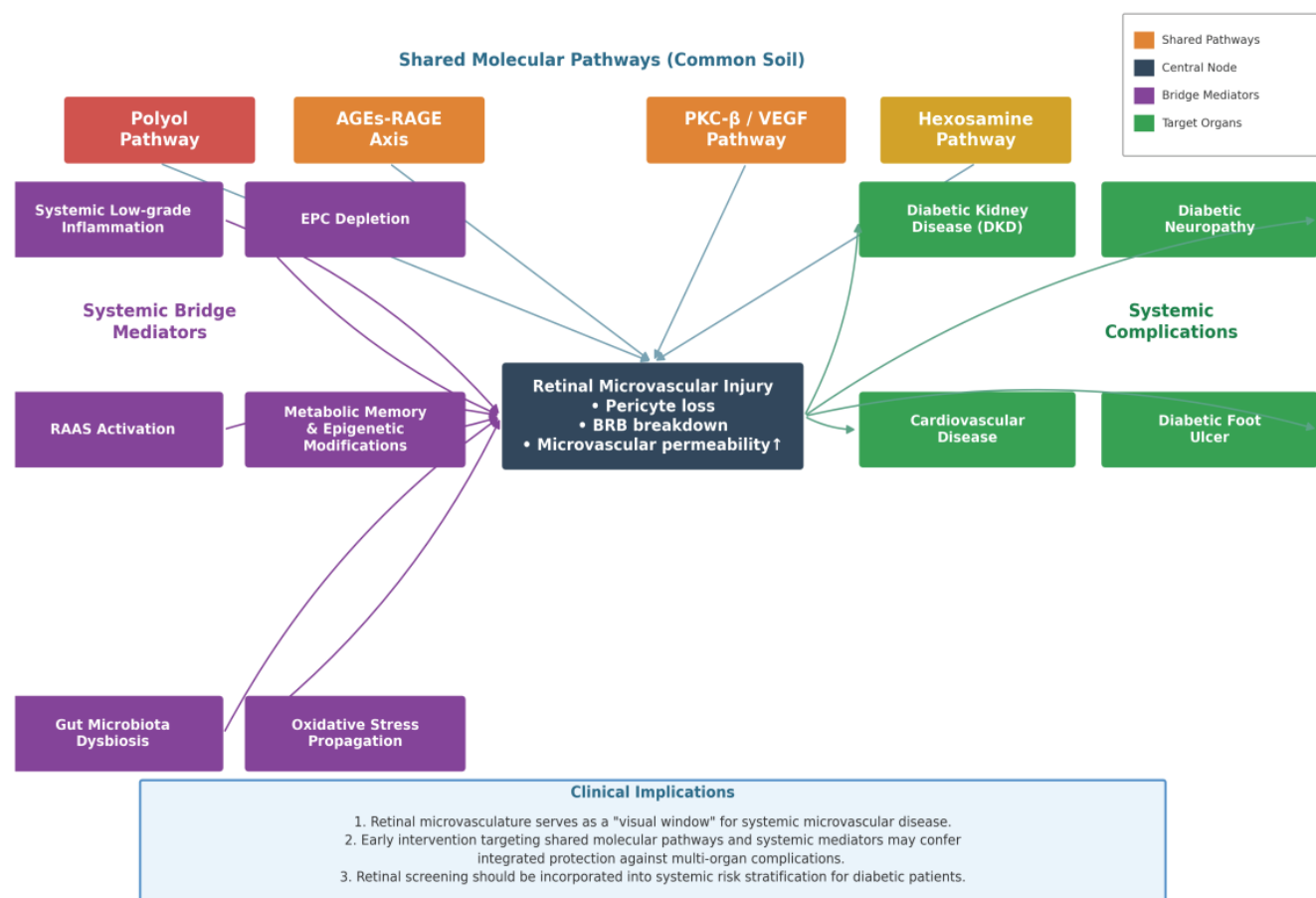
### 4.3 Systemic Propagation of Oxidative Stress and Mitochondrial Dysfunction

Mitochondrial ROS overproduction and mtDNA damage are core elements of energy metabolic failure in retinal microvascular endothelial cells. Studies have shown that glomerular podocytes, dorsal root ganglion neurons, and cardiomyocytes similarly exhibit ETC dysfunction and mtROS burst under high-glucose conditions<sup>[13,14]</sup>. More critically, damaged retinal microvascular endothelial cells release damage-associated molecular patterns (DAMPs), such as oxidatively modified lipoproteins and mtDNA fragments, into the systemic circulation, where they activate pattern recognition receptors in distant organs and promote the propagation of systemic inflammatory signals. This increase in systemic oxidative stress load represents an important mechanism explaining the association between retinal microvascular injury and cardiovascular events and all-cause mortality.

### 4.4 Systemic Cascade of Chronic Inflammatory Networks

Inflammatory mediators including IL-1 $\beta$ , IL-18, and TNF- $\alpha$  produced by local NLRP3 inflammasome activation and NF- $\kappa$ B signal amplification in the retina can enter the systemic circulation through the disrupted BRB, forming a “retina-systemic” inflammatory axis. Elevated circulating IL-1 $\beta$  and TNF- $\alpha$  further activate inflammatory signals in glomerular endothelial cells, nerve endoneurial macrophages, and coronary artery endothelial cells, promoting the progression of systemic target-organ microvascular injury<sup>[18]</sup>. Furthermore, chronic retinal inflammation can influence systemic immune regulation through the vagus nerve-spleen axis and the hypothalamic-pituitary-adrenal axis, constituting a neuro-immune-endocrine network-mediated systemic inflammatory amplification effect<sup>[16]</sup>.

*Figure 2. The “Retina-Systemic” Microvascular Network and Systemic Bridge Mediators*



## 5. Systemic Bridge Mediators: Key Mechanisms Linking Retinal Injury to Systemic Complications

Beyond shared molecular pathways, several key systemic bridge mediators exist between retinal microvascular injury and systemic complications. Serving as “messengers” connecting local retinal pathology to systemic multi-organ damage, these mediators play pivotal roles in the coordinated onset and progression of complications.

### 5.1 Systemic Low-Grade Inflammation and Circulating Inflammatory Mediators

DR, particularly proliferative DR (PDR), is closely associated with a systemic low-grade inflammatory state. PDR patients demonstrate significantly elevated levels of IL-6, TNF- $\alpha$ , IL-1 $\beta$ , MCP-1, and C-reactive protein (CRP) in both vitreous and peripheral blood. These inflammatory mediators not only reflect the severity of local retinal inflammation but also mediate systemic vascular endothelial dysfunction through the systemic circulation: promoting monocyte adhesion, enhancing platelet aggregability, and activating the coagulation cascade, thereby increasing the risk of atherosclerotic cardiovascular events<sup>[18]</sup>. Clinical studies have shown that the presence of DR is independently associated with subclinical inflammatory marker levels, suggesting that retinal microvascular injury may serve as an “amplifier” and “indicator” of systemic inflammatory status.

### 5.2 Circulating Endothelial Progenitor Cell (EPC) Depletion and Vascular Repair Impairment

Endothelial progenitor cells (EPCs), derived from bone marrow, participate in physiological and pathological vascular repair. DR patients exhibit significantly decreased numbers and function of circulating EPCs, manifesting as diminished proliferative, migratory, and vasculogenic capacities. EPC depletion not only impairs vascular repair capacity in retinal ischemic areas, exacerbating non-perfusion zone expansion and neovascularization, but also leads to insufficient endothelial repair reserves in the systemic microvascular system. Studies have shown that reduced EPC levels are significantly associated with increased carotid intima-media thickness, coronary endothelial dysfunction, and delayed healing of diabetic foot ulcers<sup>[30]</sup>. Therefore, EPC depletion constitutes an important cellular bridge connecting retinal microvascular injury to systemic vascular repair impairment.

### 5.3 Renin-Angiotensin-Aldosterone System (RAAS) Activation

RAAS plays a central role in the development and progression of both DR and DKD. Retinal vascular endothelial cells and pericytes express angiotensin II (Ang II) type 1 receptors (AT1R), through which Ang II activates NADPH oxidase, promotes VEGF expression, and induces endothelial cell apoptosis. Systemic RAAS activation not only directly damages glomerular hemodynamics (efferent arteriolar constriction, intraglomerular hypertension) but also exacerbates retinal microvascular injury by promoting systemic oxidative stress and inflammatory responses<sup>[31]</sup>. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) have demonstrated dual protective effects on both the kidney and retina in DR and DKD<sup>[32,33]</sup>, confirming the value of RAAS as a cross-organ bridge mediator and therapeutic target.

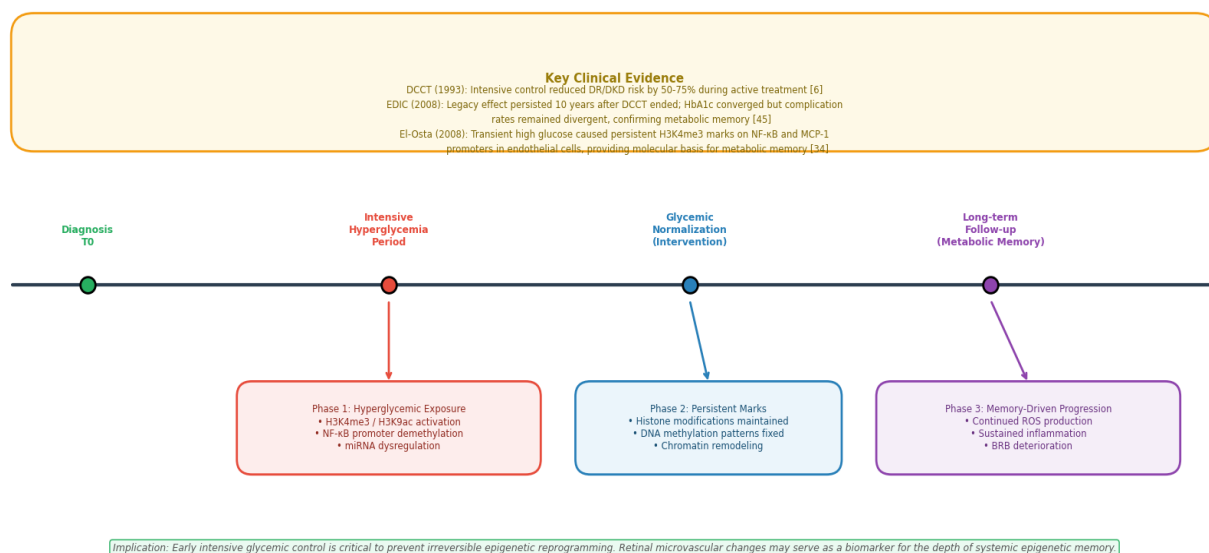
#### 5.4 Metabolic Memory and Epigenetic Modifications

The phenomenon of “metabolic memory” refers to the persistent driving of complication progression by prior hyperglycemic exposure even after blood glucose normalization. Its molecular basis lies in epigenetic modifications, including histone methylation and acetylation, DNA methylation, and non-coding RNA regulation. In retinal microvascular endothelial cells, hyperglycemia-induced alterations in histone lysine residue modifications (such as H3K4 trimethylation and H3K9 acetylation, which are transcriptional activation marks) can persistently promote the transcription of pro-inflammatory genes such as NF- $\kappa$ B<sup>[34-36]</sup>. Similar epigenetic imprints have also been confirmed in glomerular mesangial cells, cardiomyocytes, and vascular endothelial cells. This cross-organ epigenetic “memory” implies that the severity of retinal microvascular injury may reflect the depth of epigenetic reprogramming in systemic target organs, providing an epigenetic basis for DR as a predictor of systemic complication risk.

#### 5.5 Gut Microbiota Dysbiosis and Systemic Metabolic-Immune Interactions

Recent research has revealed the emerging role of the “gut-retina axis” in DR. Diabetic patients exhibit gut microbiota dysbiosis characterized by reduced Firmicutes/Bacteroidetes ratio, decreased butyrate-producing bacteria, and increased opportunistic pathogens. Impaired intestinal barrier function leads to the translocation of bacterial products such as lipopolysaccharide (LPS) into the bloodstream, activating systemic Toll-like receptor 4 (TLR4)/NF- $\kappa$ B inflammatory signals and exacerbating retinal microvascular inflammation<sup>37</sup>. Concurrently, gut microbiota metabolites (such as short-chain fatty acids, trimethylamine N-oxide, and bile acids) influence retinal and systemic microvascular function by modulating systemic immune homeostasis and vascular tone<sup>[38]</sup>. Gut microbiota dysbiosis thus constitutes a novel systemic bridge connecting local retinal pathology to systemic metabolic-immune imbalance.

Figure 5. Metabolic Memory: Persistent Epigenetic Programming Beyond Glycemic Control



## 6. Predictive Value of Retinal Vascular Parameters for Systemic Complications

As the only microvascular bed directly observable in vivo through non-invasive means, the retina provides a unique and rich source of information for assessing systemic microcirculatory status and complication risk. Extensive epidemiological and clinical studies have confirmed that the presence and severity of DR possess independent predictive value for major systemic

complications.

### 6.1 Association of DR Staging with Nephropathy and Cardiovascular Event Risk

Multiple large-scale cohort studies and meta-analyses have demonstrated a significant positive graded association between DR and DKD. Non-proliferative DR (NPDR) patients show significantly increased risks of microalbuminuria and macroalbuminuria compared with those without retinopathy; PDR patients face further elevated risks of progression to end-stage kidney disease <sup>[39]</sup>. This association is independent of traditional risk factors including glycated hemoglobin (HbA1c), diabetes duration, and blood pressure <sup>[25]</sup>, suggesting that the degree of retinal microvascular injury may serve as a clinical surrogate indicator for renal microvascular disease.

In the cardiovascular domain, DR (especially PDR and that coexisting with macular edema) is significantly associated with coronary heart disease, heart failure, and cardiovascular mortality. DR patients demonstrate significantly higher incidence of coronary microvascular dysfunction than those without retinopathy, and the number of retinal microaneurysms positively correlates with coronary artery calcium scores <sup>[40]</sup>. The UK Prospective Diabetes Study (UKPDS) and multiple subsequent studies have confirmed that DR is an independent predictor of cardiovascular events in patients with type 2 diabetes mellitus, with incremental predictive value beyond traditional risk factors <sup>[7]</sup>.

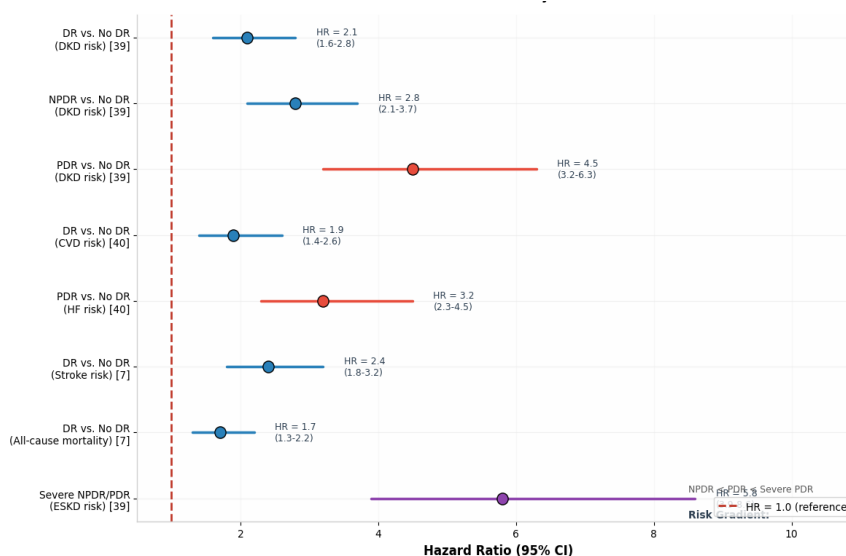
### 6.2 Retinal Vascular Geometric Parameters and Systemic Microcirculatory Assessment

Beyond DR staging, quantitative retinal vascular analysis provides more refined systemic microvascular assessment indices. Narrowed retinal arteriolar diameter, reduced arteriovenous diameter ratio, and decreased vascular fractal dimension reflect simplification of the systemic microvascular arborization, and are associated with hypertensive target-organ damage, insulin resistance, and inflammatory marker levels. Widened retinal venular diameter is associated with systemic endothelial dysfunction, increased blood viscosity, and elevated cardiovascular event risk <sup>[41,42]</sup>. These geometric parameters, obtainable through non-invasive fundus imaging techniques, provide quantifiable tools for systemic microvascular risk stratification in diabetic patients.

### 6.3 Expanded Applications of Optical Coherence Tomography Angiography (OCTA)

Optical coherence tomography angiography (OCTA) technology enables three-dimensional visualization of retinal and choroidal capillaries at micrometer-level resolution <sup>[43,44]</sup>. OCTA parameters—including reduced macular vascular density, enlarged foveal avascular zone (FAZ) area, and decreased deep capillary plexus perfusion—are not only closely associated with DR severity but also significantly correlate with systemic endothelial function indices such as flow-mediated vasodilation (FMD). Enlarged FAZ area is considered an early marker of systemic microvascular rarefaction and may predict systemic complication risk before the appearance of traditional DR signs. The clinical application of OCTA technology is driving the transition of retinal microvascular assessment from qualitative staging to quantitative functional evaluation.

Figure 3. Association Between Diabetic Retinopathy Stage and Systemic Complication Risk (Pooled Hazard Ratios from Major Cohort Studies)



## 7. Clinical Intervention Strategies from the “Retina-Systemic” Network Perspective

Based on the deep interconnections between retinal microvascular injury and systemic complications at the mechanistic, structural, and systemic mediator levels, clinical intervention strategies should shift from single target-organ protection toward integrated prevention and management of the “retina-systemic” network. The following sections elaborate on this approach from four dimensions: metabolic control, targeting shared pathways, anti-inflammatory and antioxidant therapy, and screening strategies.

### 7.1 Intensive Glycemic Control and Metabolic Memory Reversal

Strict glycemic control is the cornerstone of preventing DR and systemic complications. The Diabetes Control and Complications Trial (DCCT) and its long-term follow-up study, the Epidemiology of Diabetes Interventions and Complications (EDIC), confirmed that intensive glycemic control significantly reduces the risk of DR and DKD, and that this protective effect persists after cessation of intensive intervention (the “legacy effect”), suggesting that early optimal glycemic control can reverse or attenuate the epigenetic imprint of metabolic memory<sup>[6,45]</sup>. For patients with established DR, achieving glycemic targets as early as possible and avoiding glycemic variability are critical for blocking metabolic memory-driven systemic complication progression. Sodium-glucose cotransporter 2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP-1RA) have demonstrated significant protective effects on diabetic kidney complications and major adverse cardiovascular events (MACE) in large cardiovascular outcome trials<sup>[46-49]</sup>, and exploratory analyses of some agents have suggested potential effects on DR progression.

### 7.2 Integrated Intervention Targeting Shared Molecular Pathways

Given the shared activation of the polyol pathway, AGEs-RAGE axis, PKC- $\beta$ /VEGF pathway, and RAAS in retinal and systemic target organs, intervention strategies targeting these shared pathways possess integrative prevention and treatment potential. ACEI/ARB drugs, which inhibit RAAS while reducing both DR progression risk and DKD incidence, represent a classic paradigm of integrated prevention and management<sup>[32,33]</sup>. Anti-VEGF agents (such as ranibizumab, aflibercept, and conbercept) are administered via intravitreal injection for DR treatment, while changes in systemic VEGF levels and their potential effects on cardiovascular and renal microvasculature are receiving increasing attention. Upstream metabolic pathway-targeting drugs such as aldose reductase inhibitors, AGE breakers, and RAGE antagonists, although yielding mixed results in clinical trials, remain important directions for future integrated intervention<sup>[27]</sup>.

### 7.3 Systemic Effects of Anti-Inflammatory and Antioxidant Therapy

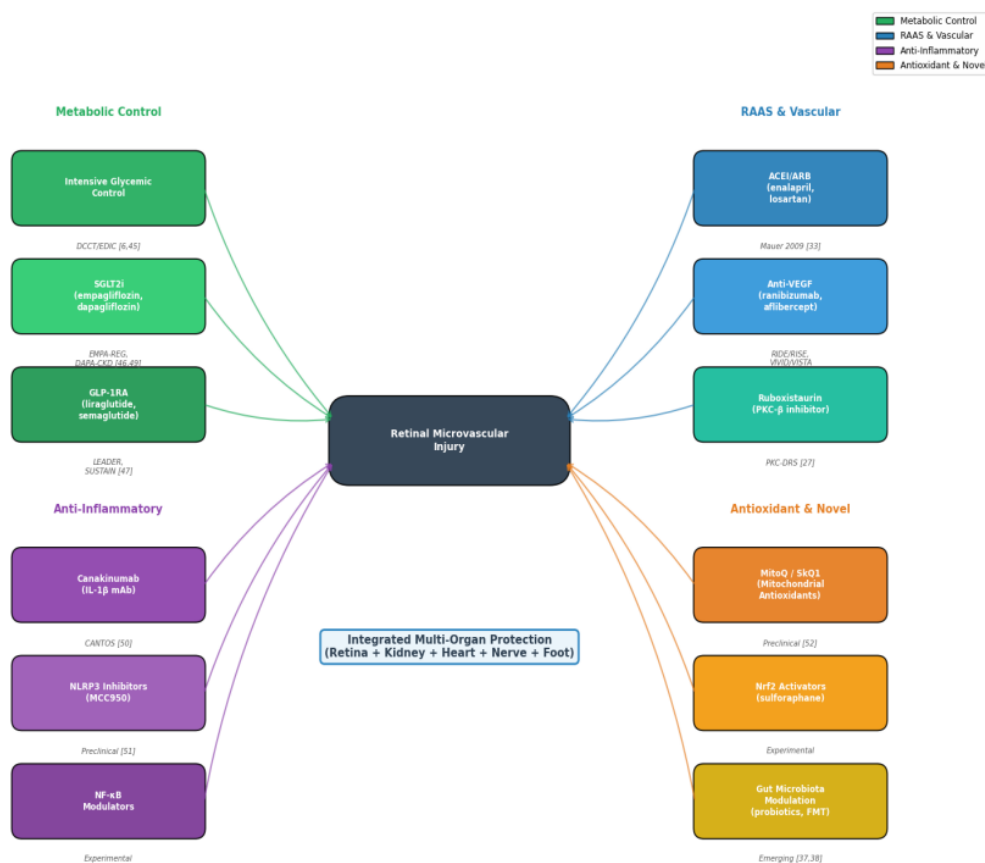
Given that chronic inflammation and oxidative stress constitute the common core mechanisms of retinal and systemic complications, anti-inflammatory and antioxidant therapies possess a theoretical basis for cross-organ protection. The IL-1 $\beta$  monoclonal antibody canakinumab demonstrated potential for reducing high-sensitivity C-reactive protein (hs-CRP) levels and cardiovascular events in the CANTOS cardiovascular outcomes trial, suggesting that IL-1 $\beta$  pathway inhibition may confer systemic microvascular protective effects<sup>[50]</sup>. NLRP3 inflammasome inhibitors (such as MCC950) and NF- $\kappa$ B pathway modulators have shown protective effects on retinal and renal microvasculature in animal models<sup>[51]</sup>. Regarding antioxidant therapy, mitochondria-targeted antioxidants (such as MitoQ and SkQ1) and Nrf2 pathway activators, which improve mitochondrial function and enhance endogenous antioxidant defenses, may simultaneously benefit retinal and systemic microvascular systems<sup>[52]</sup>.

### 7.4 Retinal Screening as a Tool for Systemic Complication Risk Stratification

Based on the strong association between DR and systemic complications, systematic retinal screening should transcend the realm of ophthalmology to become a tool for systemic risk stratification in the comprehensive management of diabetes. For patients with confirmed DR, particularly those with PDR or severe NPDR, enhanced monitoring of renal function (urinary albumin-to-creatinine ratio, estimated glomerular filtration rate), cardiovascular risk assessment (electrocardiography, echocardiography, and coronary artery calcium scoring), and neurological examination (vibration perception threshold, nerve conduction velocity) is warranted. Conversely, for diabetic patients with established DKD or cardiovascular disease, comprehensive dilated fundus examination should be performed even in the absence of retinopathy symptoms<sup>[5]</sup>. The development of artificial intelligence (AI)-assisted fundus image analysis technology enables large-scale, low-cost retinal

screening and systemic risk prediction, potentially driving a paradigm shift in diabetic complication prevention and control from passive treatment to active prediction.

Figure 4. Integrated Intervention Targets from the “Retina-Systemic” Network Perspective



## 8. Conclusion

Hyperglycemia-induced retinal microvascular injury is a systematic pathological process initiated by metabolic stress, amplified by oxidative stress, driven by inflammatory responses, and mediated by hemodynamic disturbances. The metabolic network activation of the polyol pathway, AGEs-RAGE axis, PKC-β, and hexosamine pathway constitutes the initiating link of injury; mitochondrial dysfunction and antioxidant system depletion form the core hub of oxidative damage; NLRP3 inflammasome, NF-κB, and innate immune cell activation establish the pathological foundation of chronic inflammation; and NO/ET-1 imbalance, tight junction degradation, and pericyte apoptosis ultimately lead to BRB disruption and microvascular structural remodeling.

Retinal microvasculature shares high structural homology with glomerular, nerve endoneurial, and lower-extremity microvessels in basement membrane structure, pericyte coverage, and barrier function, rendering retinal microvascular injury not merely an ocular complication of diabetes but an important component and “visual window” of systemic microvascular disease. Systemic low-grade inflammation, EPC depletion, RAAS activation, metabolic memory, epigenetic modifications, and gut microbiota dysbiosis serve as critical systemic bridge mediators that mediate or predict the deep associations between retinal injury and systemic multi-organ complications. Retinal vascular parameters and DR staging possess independent predictive value for the risk of nephropathy, cardiovascular events, and other systemic complications.

Therefore, based on the “retina-systemic” microvascular network perspective, incorporating retinal screening into the systemic complication risk stratification system for diabetes and implementing early integrated interventions targeting the shared molecular pathways and systemic mediators of hyperglycemia-induced microvascular injury hold significant theoretical importance and clinical application value for the coordinated prevention and control of diabetic multi-organ complications. Future research should further focus on the epigenetic regulatory mechanisms of cross-organ microvascular injury, the interactive network of the gut microbiota-retina-systemic metabolism axis, and the construction and validation of

AI-based retina-systemic risk prediction models, with the goal of achieving precise integrated prevention and management of diabetic complications.

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No

## Conflict of Interests

The authors declare that there is no conflict of interest regarding the publication of this paper.

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## FIGURE LEGENDS

Figure 1. Molecular network of hyperglycemia-induced retinal microvascular injury. Chronic hyperglycemia activates four metabolic stress pathways (the polyol pathway, the AGEs-RAGE axis, PKC- $\beta$  activation, and the hexosamine pathway), which converge on oxidative stress with mitochondrial injury and chronic inflammation; the two hubs amplify each other through a positive feedback loop. These mechanisms drive pericyte loss, tight junction disruption, and hemodynamic alteration, culminating in blood-retinal barrier (BRB) breakdown and the characteristic lesions of diabetic retinopathy, including microaneurysm, retinal edema and exudates, and neovascularization in proliferative diabetic retinopathy. AR, aldose reductase; AGEs, advanced glycation end products; RAGE, receptor for AGEs; DAG, diacylglycerol; VEGF, vascular endothelial growth factor; UDP-GlcNAc, uridine diphosphate N-acetylglucosamine; ETC, electron transport chain; mtROS, mitochondrial reactive oxygen species; mtDNA, mitochondrial DNA; NLRP3, NOD-like receptor protein 3; NF- $\kappa$ B, nuclear factor-kappa B; IL, interleukin; TNF- $\alpha$ , tumor necrosis factor-alpha; ET-1, endothelin-1; eNOS, endothelial nitric oxide synthase; MLCK, myosin light chain kinase; PDGF-BB, platelet-derived growth factor-BB; PDGFR- $\beta$ , platelet-derived growth factor receptor- $\beta$ ; NO, nitric oxide; BRB, blood-retinal barrier.

Table 1. Structural homology between retinal microvasculature and systemic target organs. The table compares retinal, glomerular, nerve endoneurial, and lower-extremity microvessels across seven dimensions: basement membrane components, pericytes/mesangial cells, barrier type, tight junction/slit diaphragm proteins, main injury manifestations under hyperglycemia, shared core signaling pathways, and common pathological outcomes. BRB, blood-retinal barrier; GFB, glomerular filtration barrier; BNB, blood-nerve barrier; TJ, tight junction; SD, slit diaphragm.

Figure 2. The “retina-systemic” microvascular network and systemic bridge mediators. The four shared molecular pathways (polyol pathway, AGEs-RAGE axis, PKC- $\beta$ /VEGF pathway, and hexosamine pathway) converge on retinal microvascular injury (center), which is bidirectionally linked to six systemic bridge mediators (left): systemic low-grade inflammation, EPC depletion, RAAS activation, metabolic memory and epigenetic modifications, gut microbiota dysbiosis, and oxidative stress

propagation. These mediators facilitate the progression of retinal injury toward four major systemic complications (right): diabetic kidney disease (DKD), diabetic neuropathy, cardiovascular disease, and diabetic foot ulcer. The dashed arrows indicate indirect systemic effects mediated through circulating factors. AGEs, advanced glycation end products; RAGE, receptor for AGEs; PKC- $\beta$ , protein kinase C-beta; VEGF, vascular endothelial growth factor; EPC, endothelial progenitor cell; RAAS, renin-angiotensin-aldosterone system; BRB, blood-retinal barrier.

Figure 3. Association between diabetic retinopathy stage and systemic complication risk. Pooled hazard ratios (HRs) with 95% confidence intervals from major cohort studies are shown for diabetic kidney disease (DKD), cardiovascular disease (CVD), heart failure (HF), stroke, and all-cause mortality in patients with versus without diabetic retinopathy (DR), as well as for severe non-proliferative diabetic retinopathy (NPDR)/proliferative diabetic retinopathy (PDR) versus NPDR (reference, HR = 1.0) regarding end-stage kidney disease (ESKD) risk. The presence and severity of DR are associated with graded increases in the risk of systemic complications, independent of traditional risk factors.

Figure 4. Integrated intervention targets from the “retina-systemic” network perspective. Candidate interventions are grouped into four categories: metabolic control (intensive glycemic control, sodium-glucose cotransporter 2 inhibitors [SGLT2i], and glucagon-like peptide-1 receptor agonists [GLP-1RA]), RAAS and vascular protection (angiotensin-converting enzyme inhibitors [ACEIs]/angiotensin II receptor blockers [ARBs], anti-VEGF agents, and PKC- $\beta$  inhibitors), anti-inflammatory strategies (canakinumab, NLRP3 inflammasome inhibitors, and NF- $\kappa$ B modulators), and antioxidant and novel therapies (mitochondria-targeted antioxidants, Nrf2 pathway activators, and epigenetic modulators). These targets converge on retinal microvascular injury and provide integrated multi-organ protection spanning the retina, kidney, heart, nerve, and foot. RAAS, renin-angiotensin-aldosterone system; VEGF, vascular endothelial growth factor; PKC- $\beta$ , protein kinase C-beta; NLRP3, NOD-like receptor protein 3; NF- $\kappa$ B, nuclear factor-kappa B; Nrf2, nuclear factor erythroid 2-related factor 2.

Figure 5. Metabolic memory: persistent epigenetic programming beyond glycemic control. Key clinical evidence includes the Diabetes Control and Complications Trial (DCCT, 1993), showing that intensive control reduced the risk of retinopathy complications; its long-term follow-up (EDIC, 2008), demonstrating a persistent legacy effect ten years after the trial ended despite converged HbA1c levels; and El-Osta et al. (2008), showing that transient high glucose induces persistent H3K4me3 marks on the NF- $\kappa$ B and MCP-1 promoters. The timeline depicts three phases: phase 1, hyperglycemic exposure, with H3K4me3/H3K9ac activation, NF- $\kappa$ B promoter demethylation, and miRNA dysregulation; phase 2, glycemic normalization, during which histone modifications are maintained, DNA methylation patterns remain fixed, and chromatin remodeling persists; and phase 3, memory-driven progression, characterized by continued reactive oxygen species (ROS) production, sustained inflammation, and blood-retinal barrier (BRB) deterioration. Early intensive glycemic control is critical to prevent irreversible epigenetic reprogramming, and retinal microvascular changes may serve as a biomarker for the depth of systemic epigenetic memory. HbA1c, glycated hemoglobin; H3K4me3, histone H3 lysine 4 trimethylation; H3K9ac, histone H3 lysine 9 acetylation; NF- $\kappa$ B, nuclear factor-kappa B; MCP-1, monocyte chemoattractant protein-1; miRNA, microRNA; T0, time of diagnosis.