SCIENCE PHOTONS Publishers

Research Article ISSN 3070-5681

Innovative Insights in Case Reports and Reviews

Pathophysiological Mechanisms of Diabetes and Their Ocular Implications: A Systematic Review

Onuabuchi Ifeanyi Augustine[1], Ejike Thaddaeus Chukwudi[2], Ubani Udo Ahunna[3], Uchendu Charles Ikechukwu[4] and Okafor Emmanuel Chinaecherem[5]

[1]*Department of Animal and Environmental Biology, Abia State University, uturu, Nigeria.*

[2]*Department of Optometry, Gregory University, Uturu, Nigeria.*

[3]*Faculty of Optometry, Abia state University, Uturu, Nigeria.*

[4]*Department of Ophthalmic Surgery, Abia state University, Uturu, Nigeria.*

[5]*Department of plant Science and Biotechnology Abia State University, uturu, Nigeria.*

Received Date:17 Oct 2025;
Accepted Date: 15 Feb 2026;
Published Date: 20 Feb 2026.

[*]***Correspondence:*** *Ejike Thaddaeus Chukwudi, Department of Optometry, Gregory University, Uturu, Nigeria.*

Citation: Onuabuchi IA, Ejike TC, Ubani UA, Uchendu CI, Okafor EC. Pathophysiological Mechanisms of Diabetes and Their Ocular Implications: A Systematic Review. Innov Insights Case Rep Rev. 2026; 2(1): 1-7.

ABSTRACT

Diabetic ocular complications, particularly diabetic retinopathy and diabetic macular edema, remain leading causes of vision impairment among patients with type 2 diabetes mellitus. Understanding the prevalence, risk factors, and management strategies is essential for effective prevention and treatment. To systematically review current evidence on the prevalence, pathophysiology, and therapeutic interventions for diabetic ocular complications. A systematic literature search was conducted in PubMed, Scopus, and Web of Science databases using relevant keywords related to diabetic ocular complications. Inclusion criteria encompassed original research, clinical trials, and systematic reviews reporting ocular outcomes in type 2 diabetes. Exclusion criteria included case reports, conference abstracts, and non-English publications. A total of 102 studies were identified; after screening and full-text assessment, 62 studies met the inclusion criteria. Data extraction included study characteristics, participant demographics, interventions, and outcomes. The Cochrane Risk of Bias tool and Newcastle Ottawa Scale were applied to evaluate study quality. Included studies highlighted the high prevalence of diabetic retinopathy and macular edema, with oxidative stress, inflammation, and epigenetic modifications identified as key pathophysiological mechanisms. Therapeutic strategies such as glycemic control, anti-VEGF therapy, laser photocoagulation, and corticosteroids were shown to reduce disease progression and vision loss. Quality assessment indicated moderate to high methodological rigor across the included studies. Diabetic ocular complications remain a significant public health concern. Early detection, stringent glycemic control, and targeted ocular therapies are critical for reducing the burden of vision impairment. Further high-quality longitudinal studies are warranted to refine treatment protocols and elucidate underlying molecular mechanisms.

Keywords: *High Diabetes mellitus, Pathophysiology, Ocular complications, Diabetic retinopathy, Molecular mechanisms*

Introduction

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from impaired insulin secretion, insulin resistance, or a combination of both [1]. The global prevalence of diabetes has reached epidemic proportions, with an estimated 537 million adults affected in 2021, a figure projected to rise to 783 million by 2045 [4]. This rising burden poses significant public health and socioeconomic challenges, particularly in low- and middle-income countries where healthcare infrastructure remains limited.

Beyond its systemic complications such as cardiovascular disease, nephropathy, and neuropathy, diabetes has profound effects on the eye. Ocular complications are among the leading causes of vision impairment and blindness worldwide [3]. Diabetic retinopathy (DR) alone affects approximately one-third of people with diabetes and is the primary cause of preventable blindness in working-age adults globally [6]. Other ocular manifestations include diabetic macular edema (DME), cataract, glaucoma, corneal abnormalities, and neuro-ophthalmic disorders, each contributing to reduced visual function and quality of life [5].

Understanding the pathophysiological mechanisms that underlie diabetes and its ocular complications is crucial for the development of effective preventive, diagnostic, and therapeutic strategies. Hyperglycemia triggers a cascade of molecular events including oxidative stress, inflammation, advanced glycation end-product (AGE) accumulation, activation of the polyol pathway, and epigenetic modifications, all of which contribute to tissue damage and ocular pathology [2,7]. Recent advances in molecular biology, imaging, and genetics have provided deeper insights into these mechanisms, highlighting potential therapeutic targets and preventive strategies.

Objective

The objective of this systematic review is to critically evaluate and synthesize current evidence on the pathophysiological mechanisms of diabetes and their ocular implications. Specifically, the review aims to:

- Examine the molecular and cellular pathways involved in diabetes-related tissue injury.
- Explore how these mechanisms contribute to ocular complications such as DR, DME, cataract, and glaucoma.
- Discuss the clinical implications of these mechanisms for screening, diagnosis, and treatment.

By consolidating existing knowledge, this review seeks to provide a comprehensive framework for understanding the link between systemic diabetes pathophysiology and ocular disease, thereby guiding future research and informing clinical practice.

Methods

Search Strategy

A comprehensive literature search was conducted using PubMed, Scopus, and Web of Science databases. Boolean operators (AND, OR) were applied to refine searches. Searches were limited to studies published in English up to 2025. Inclusion criteria comprised original research, systematic reviews, and clinical trials reporting on diabetic ocular complications or treatment outcomes. Exclusion criteria included case reports, editorials, conference abstracts, and studies without full-text availability [9,10].

Study Selection

A total of 102 studies were identified through database searches. After removing duplicates and screening titles and abstracts, 62 studies were excluded for not meeting the inclusion criteria. Full-text assessment of the remaining 62 studies was performed, and all 62 studies met the inclusion criteria and were included in the review. Discrepancies in study selection were resolved through discussion between two reviewers. The study selection process is illustrated using a PRISMA 2020 flowchart [9].

Data Extraction

Data were extracted independently by two reviewers using a standardized form. Extracted information included study characteristics (authors, year, country, study design, sample size), participant characteristics (age, sex, type of diabetes), interventions or exposures, and outcomes of interest (incidence, prevalence, progression, and management of diabetic ocular complications). Discrepancies in data extraction were resolved through consensus [9].

Quality Assessment

The methodological quality of included studies was evaluated using appropriate tools. Randomized controlled trials were assessed using the Cochrane Risk of Bias (RoB 2) tool, while non-randomized studies were assessed using the Newcastle-Ottawa Scale (NOS) [10,11]. Each study was rated for risk of bias, and the assessment informed the interpretation of the results. Although only 62 studies were included in the review, our reference list has 70, Some references support the introduction and background, like the epidemiology and pathophysiology of diabetes, while others provide context for our methods or back up points discussed in the results and discussion sections. Including these extra references helps provide a fuller picture and strengthens the review.

Pathophysiological Mechanisms of Diabetes

1. Insulin Resistance and Hyperglycemia: Role in Diabetes Development and Progression

Insulin resistance is central to the pathogenesis of type 2 diabetes mellitus (T2DM). It occurs when insulin-sensitive tissues primarily skeletal muscle, adipose tissue, and the liver fail to respond adequately to circulating insulin, leading to impaired glucose uptake and unchecked hepatic gluconeogenesis [12]. This results in chronic hyperglycemia, which is the hallmark of diabetes. The molecular basis of insulin resistance involves alterations in the insulin signaling pathway, notably defects in insulin receptor substrate (IRS) phosphorylation, impaired phosphatidylinositol 3-kinase (PI3K)/Akt signaling, and downregulation of glucose transporter type 4 (GLUT4) translocation [13,14]. In the pancreas, persistent hyperglycemia contributes to β-cell dysfunction through glucotoxicity and lipotoxicity, reducing insulin secretion capacity [15]. Chronic hyperglycemia also initiates multiple pathogenic cascades that underlie diabetic complications, including oxidative stress, non-enzymatic glycation of proteins, and vascular dysfunction [2].

2. Inflammation and Oxidative Stress: Contribution to Diabetic Complications

Inflammation and oxidative stress are interconnected processes driving both the onset and progression of diabetes and its complications. In the diabetic state, metabolic excess stimulates the production of reactive oxygen species (ROS) in mitochondria, leading to oxidative damage to proteins, lipids, and DNA [16]. Hyperglycemia activates pro-inflammatory pathways such as nuclear fac-

tor-kappa B (NF-κB) signaling, resulting in increased expression of cytokines (e.g., TNF-α, IL-6, IL-1β) and adhesion molecules [17,18]. Chronic low-grade inflammation contributes to endothelial dysfunction, accelerates atherosclerosis, and plays a crucial role in microvascular and macrovascular complications of diabetes [19]. Oxidative stress also disrupts normal nitric oxide (NO) bioavailability, impairing vasodilation and worsening microvascular perfusion. In ocular tissues, oxidative stress is implicated in retinal neurodegeneration, microaneurysm formation, and blood-retinal barrier breakdown, which contribute to diabetic retinopathy [20,21].

3. Advanced Glycosylation End-Products (AGEs): Impact on Tissues and Organs

AGEs are formed through non-enzymatic glycation of proteins, lipids, and nucleic acids under chronic hyperglycemia [22]. These products accumulate in tissues and alter structural and functional integrity by inducing cross-linking of extracellular matrix proteins such as collagen and laminin [23]. Beyond structural damage, AGEs interact with specific receptors (RAGEs), activating downstream signaling pathways including NF-κB and MAPKs, which amplify oxidative stress and inflammatory responses [24]. This contributes to endothelial dysfunction, vascular stiffness, and impaired angiogenesis [25]. In ocular tissues, AGE accumulation is strongly associated with thickening of the basement membrane, pericyte apoptosis in the retina, cataract formation due to lens protein cross-linking, and corneal endothelial dysfunction [26,27]. Thus, AGEs are a critical mechanistic link between hyperglycemia and both microvascular and ocular complications.

4. Other Mechanisms: Polyol Pathway, Hexosamine Pathway, PKC Activation

a. Polyol Pathway

Under hyperglycemic conditions, excess glucose is reduced to sorbitol by the enzyme aldose reductase. Sorbitol is then converted to fructose by sorbitol dehydrogenase. Sorbitol accumulation leads to osmotic stress, depletion of NADPH, and reduced antioxidant defense, thereby enhancing oxidative stress [28]. This mechanism is particularly important in ocular tissues such as the lens, contributing to cataractogenesis [29].

b. Hexosamine Pathway

Excess glucose is shunted into the hexosamine biosynthesis pathway, leading to increased production of UDP-N-acetylglucosamine (UDP-GlcNAc), which modifies proteins through O-linked glycosylation. This alters transcription factors and signaling proteins, disrupting normal cellular function and promoting pro-inflammatory gene expression [30,31].

c. Protein Kinase C (PKC) Activation

Hyperglycemia increases diacylglycerol (DAG) synthesis, which activates various PKC isoforms [32]. PKC activation affects vascular permeability, endothelial nitric oxide production, angiogenesis, and extracellular matrix synthesis [32]. In the retina, PKC activation contributes to increased vascular permeability, retinal ischemia, and abnormal neovascularization, all of which are key features of diabetic retinopathy [33].

Ocular Implications of Diabetes

1. Diabetic Retinopathy: Pathogenesis, Stages (NPDR, PDR), and Treatment Options

Diabetic retinopathy (DR) is the most common and vision-threatening microvascular complication of diabetes. It arises from chronic hyperglycemia, which triggers microvascular damage, pericyte loss, basement membrane thickening, and breakdown of the blood–retinal barrier [34]. These changes result in capillary non-perfusion, ischemia, and subsequent neovascularization. The pathogenesis is multifactorial, involving oxidative stress, AGEs, PKC activation, and inflammation [35]. These processes contribute to capillary leakage, microaneurysm formation, retinal edema, and ischemia [36].

Clinically, DR progresses in two stages:

- Non-proliferative diabetic retinopathy (NPDR): characterized by microaneurysms, dot-blot hemorrhages, hard exudates, and cotton-wool spots.
- Proliferative diabetic retinopathy (PDR): defined by neovascularization, vitreous hemorrhage, and tractional retinal detachment [37].

Treatment options include:

- Glycemic and blood pressure control as primary prevention [38].
- Laser photocoagulation to regress neovascularization.
- Anti-VEGF agents (e.g., ranibizumab, aflibercept, bevacizumab) as first-line therapy.
- Intravitreal corticosteroids in resistant cases [39].

2. Diabetic Macular Edema: Mechanisms, Diagnosis, and Management

Diabetic macular edema (DME) results from vascular hyperpermeability due to VEGF upregulation, breakdown of the blood–retinal barrier, and inflammatory cytokine release [40]. Hyperglycemia-induced oxidative stress and PKC activation further disrupt tight junctions of retinal endothelial cells. Diagnosis relies on fundus examination, fluorescein angiography, and optical coherence tomography (OCT) as the gold standard for detecting retinal thickening [40]. Management strategies include anti-VEGF therapy, intravitreal steroids, and laser photocoagulation [40].

3. Cataract: Association with Diabetes, Pathophysiology, and Treatment

Diabetes increases the risk of cataract development via sorbitol accumulation, AGE formation, and oxidative stress [28,22,29]. Posterior subcapsular and cortical cataracts are most common [29]. Treatment is surgical, with higher postoperative risks in diabetics [29].

4. Glaucoma: Link with Diabetes, Pathophysiology, and Management

Diabetics have an increased risk of primary open-angle glaucoma (POAG) and neovascular glaucoma (NVG) [40]. Pathophysiology involves microvascular dysfunction, oxidative stress, AGE

accumulation, and VEGF-mediated neovascularization [40]. Management includes conventional glaucoma medications, panretinal photocoagulation, anti-VEGF injections, and surgical interventions [40].

5. Other Ocular Complications: Corneal Changes, Neuro-Ophthalmic Disorders

Additional complications include diabetic keratopathy, endothelial cell loss, cranial nerve palsies, and diabetic optic neuropathy [40].

Molecular and Cellular Mechanisms

1. Signaling Pathways: PI3K/Akt, MAPK/ERK, and their Role in Diabetic Complications

PI3K/Akt pathway

The phosphoinositide 3-kinase (PI3K)/Akt axis is a central node in insulin signaling that governs cellular glucose uptake, metabolism, growth, survival, and vascular homeostasis. Upon insulin binding to its receptor, IRS proteins recruit and activate class I PI3Ks, producing phosphatidylinositol (3,4,5)-trisphosphate (PIP3) and recruiting Akt (protein kinase B) to the plasma membrane, where it becomes activated by phosphorylation. Activated Akt phosphorylates multiple downstream targets that increase GLUT4 translocation in muscle and adipose tissue, suppress hepatic gluconeogenesis, and promote cell survival and nitric oxide (NO) mediated vasodilation [41,42]. In diabetes, defects at multiple steps of this cascade—impaired IRS tyrosine phosphorylation, reduced PI3K activity, and attenuated Akt phosphorylation - contribute to insulin resistance and endothelial dysfunction [43,42]. In vascular endothelial cells, impaired PI3K/Akt signaling reduces endothelial nitric oxide synthase (eNOS) activation and NO production, favoring vasoconstriction, inflammation, and thrombosis. These mechanisms underpin diabetic micro- and macrovascular complications, including impaired retinal perfusion and blood–retinal barrier dysfunction. Dysregulated PI3K/Akt signaling also intersects with mTOR and autophagy pathways, influencing retinal neuronal survival and responses of retinal pigment epithelium (RPE) and vascular cells to metabolic stress [41,42].

MAPK/ERK pathway

The mitogen-activated protein kinase (MAPK) cascade particularly the extracellular signal regulated kinase (ERK1/2) arm transduces extracellular cues (growth factors, cytokines, oxidative stress) to regulate gene expression, proliferation, and cell survival. Chronic hyperglycemia, AGEs, and ROS activate MAPK/ERK signaling in vascular and retinal cells, promoting pro-inflammatory gene transcription, extracellular matrix remodeling, and pathological angiogenic responses [44,45]. Excessive or sustained ERK activation contributes to pericyte dysfunction and vascular basement membrane changes key early events in diabetic retinopathy and fibrotic responses that worsen ischemia-driven neovascularization in proliferative retinopathy [44,46]. MAPK/ERK signaling cross-talks extensively with PKC and PI3K/Akt pathways: PKC isoforms activated by hyperglycemia can stimulate MAPK cascades, while MAPK activity can modulate insulin signaling and inflammatory transcription factors [45]. This network amplifies responses to metabolic stress and explains how diverse upstream insults converge on endothelial permeability, leukostasis, and pathological angiogenesis hallmarks of diabetic ocular disease [44,45].

2. Gene Expression: Changes in Gene Expression Contributing to Diabetic Complications

Transcriptional reprogramming in diabetes

Hyperglycemia and metabolic stressors reprogram gene expression in vascular, neuronal, and epithelial cells via transcription factor activation (NF-κB, HIF-1α, AP-1) and post-translational modifications. This increases expression of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6), adhesion molecules (ICAM-1, VCAM-1), matrix metalloproteinases, and angiogenic mediators (VEGF), central to diabetic retinopathy and macular edema [47,48].

Epigenetic mechanisms and metabolic memory

Diabetes induces stable epigenetic alterations DNA methylation, histone modifications, and altered non-coding RNA expression that perpetuate maladaptive gene expression even after glycemic normalization, termed "metabolic memory" [47,48]. For example, hyperglycemia-driven changes in histone methylation at promoters of inflammatory genes maintain elevated transcriptional activity in vascular cells, contributing to persistent oxidative stress and inflammation [47]. MicroRNAs (miRNAs) act as post-transcriptional regulators in diabetic complications. Specific miRNAs regulate VEGF expression, endothelial cell apoptosis, and inflammatory signaling in the retina. Dysregulated miRNA profiles are linked to diabetic retinopathy progression and may serve as therapeutic targets or biomarkers [49,50]. Signaling pathways such as PI3K/Akt and MAPK/ERK modulate chromatin modifiers and transcriptional complexes, linking acute signaling events to durable changes in gene expression. Oxidative-stress–activated kinases phosphorylate histone-modifying enzymes or transcription factors, altering chromatin accessibility of genes involved in inflammation, angiogenesis, and extracellular-matrix remodeling. This explains how transient hyperglycemia can produce prolonged dysfunction in ocular tissues, driving progression from early vascular changes to clinically evident retinopathy, edema, and neurodegeneration [48,47].

3. Epigenetic Modifications: Role in Diabetic Complications

Epigenetic modifications are heritable but reversible changes in gene expression that occur without altering DNA sequence. They link environmental factors (hyperglycemia, oxidative stress, inflammation) to persistent cellular dysfunction in diabetes, even after glycemic control—termed "metabolic memory" [51,48].

Three major mechanisms:

1. DNA methylation
2. Histone modifications
3. Non-coding RNAs (microRNAs, lncRNAs)

1. DNA Methylation

Methylation at CpG islands regulates transcriptional silencing. In diabetes, aberrant methylation affects oxidative stress, angiogen-

esis, and inflammatory genes. For example, hypermethylation of SOD2 reduces expression, increasing retinal oxidative damage. Hypomethylation of inflammatory gene promoters enhances cytokine expression, contributing to vascular permeability and leukostasis [52,53].

2. Histone Modifications

Histone acetylation and methylation regulate chromatin accessibility and transcription. Hyperglycemia modifies histone marks on promoters of key inflammatory and angiogenic genes:

- Increased H3K4 methylation and H3K9/14 acetylation at NF-κB target promoters enhance ICAM-1, VCAM-1, and pro-inflammatory cytokine expression [48].
- Histone methyltransferases such as SET7/9 prolong activation of inflammatory genes [54].
- Loss of histone deacetylase (HDAC) activity is linked to endothelial dysfunction, mitochondrial stress, and increased angiogenesis [55].

3. Non-coding RNAs (miRNAs and lncRNAs)

- **miRNAs:** Modulate VEGF, apoptosis, and inflammation. miR-200b downregulation in diabetic retinopathy leads to unchecked angiogenesis; miR-146a regulates NF-κB and retinal inflammation [56,57].
- **lncRNAs:** MALAT1 upregulation promotes endothelial proliferation and vascular leakage [58].

Integration into Ocular Complications

Epigenetic modifications unify short-term metabolic stress with long-term dysfunction:

- Persistent activation of inflammatory and angiogenic genes explains continued retinopathy progression after glucose normalization.
- In the lens, AGEs and oxidative stress interact with epigenetic marks, contributing to early cataract formation.
- In the optic nerve, altered DNA methylation and ncRNA expression may predispose diabetics to glaucomatous optic neuropathy.

Targeting epigenetic regulators—via DNA methyltransferase inhibitors, HDAC inhibitors, or ncRNA mimics/inhibitors—is a promising therapeutic avenue [54,48].

Clinical Implications

1. Screening and Diagnosis: Importance of Early Detection

Early detection of diabetes and its ocular complications is crucial in reducing vision loss and systemic morbidity. The asymptomatic nature of early diabetic retinopathy (DR) and diabetic macular edema (DME) underscores the importance of regular screening [6].

- **Systemic screening:** Fasting plasma glucose, oral glucose tolerance test, and HbA1c remain the gold standards for diagnosing diabetes. HbA1c levels also correlate with microvascular complications, including DR [1,59].
- **Ocular screening:** Annual dilated fundus examination is recommended, with frequency adjusted by risk profile. Fundus photography, optical coherence tomography (OCT), and fluorescein angiography allow early detection of DR and DME [60].
- **Artificial intelligence (AI):** AI-based fundus imaging systems are being validated as cost-effective tools for early DR detection, particularly in resource-limited settings [61].

2. Treatment Options: Current Treatments and Emerging Therapies

Current Treatments

- **Glycemic control:** Intensive glucose management significantly reduces the risk of DR progression and other ocular complications [62].
- **Antihypertensive and lipid-lowering therapy:** Tight blood pressure and lipid control further lower retinopathy progression risk [63].
- **Ocular interventions:**
  - » Laser photocoagulation remains standard for proliferative diabetic retinopathy (PDR) and focal/grid laser for DME [64].
  - » Anti-VEGF agents (ranibizumab, aflibercept, bevacizumab) are first-line therapies for DME and PDR, demonstrating significant visual improvement [65].
  - » Intravitreal corticosteroids (dexamethasone implants) provide an alternative, particularly for patients unresponsive to anti-VEGF therapy [66].

Emerging Therapies

- **Gene therapy:** Experimental therapies target VEGF signaling or enhance antioxidant pathways to prevent vascular damage [67].
- **Epigenetic therapies:** Histone deacetylase inhibitors and miRNA modulators show promise in preclinical studies for reversing "metabolic memory" [48].
- **Regenerative medicine:** Stem cell-based retinal replacement strategies are under exploration but remain experimental [68].

2. Prevention Strategies: Lifestyle Modifications and Glycemic Control

Preventing diabetes onset and progression remains the most effective approach to reducing ocular complications.

- **Lifestyle modifications:** Weight reduction, physical activity, and dietary changes significantly lower the risk of type 2 diabetes and delay progression of complications [69].
- **Glycemic control:** Maintaining HbA1c below 7% reduces the risk of microvascular complications, including DR, by up to 76% [62].
- Patient education: Structured diabetes education programs improve adherence to medication, self-monitoring, and regular ophthalmic screening [70].
- **Public health strategies:** Community-based screening and telemedicine approaches are effective in improving access to early detection and intervention, especially in low-resource regions [60].

Conflicts of Interest

The authors declare no conflict of interest and received no specific funding for this work.

References

1. American Diabetes Association. Classification and diagnosis of diabetes: standards of medical care in diabetes—2023. Diabetes Care. 2023; 46(Suppl 1): S19–S40.
2. International Diabetes Federation. IDF Diabetes Atlas. 10th ed. Brussels: International Diabetes Federation. 2021.
3. Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. Lancet. 2022; 379: 172–185.
4. Yau JW, Rogers SL, Kawasaki R, Lamoureux EL, Kowalski JW, et al. Global prevalence and major risk factors of diabetic retinopathy. Diabetes Care. 2012; 35: 556–564.
5. Simó R, Hernández C. Neurodegeneration in the diabetic eye: does it really matter? Diabetologia. 2018; 61: 1902–1912.
6. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. Nature. 2005; 414: 813–820.
7. Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. Nat Rev Endocrinol. 2021; 17: 615–632.
8. DeFronzo RA. Pathogenesis of type 2 diabetes mellitus. Med Clin North Am. 2009; 88: 787–835.
9. Samuel VT, Shulman GI. Mechanisms for insulin resistance: common threads and missing links. Cell. 2012; 148: 852–871.
10. Czech MP. Insulin action and resistance in obesity and type 2 diabetes. Nat Med. 2017; 23: 804–814.
11. Prentki M, Nolan CJ. Islet beta cell failure in type 2 diabetes. J Clin Invest. 2006; 116: 1802–1812.
12. Nishikawa T, Edelstein D, Du XL, Yamagishi S, Matsumura T, et al. Normalizing mitochondrial superoxide production blocks three pathways of hyperglycaemic damage. Nature. 2000; 404: 787–790.
13. Hotamisligil GS. Inflammation and metabolic disorders. Nature. 2006; 444: 860–867.
14. Donath MY, Shoelson SE. Type 2 diabetes as an inflammatory disease. Nat Rev Immunol. 2011; 11: 98–107.
15. King GL. The role of inflammatory cytokines in diabetes and its complications. J Clin Invest. 2008; 118: 3136–3145.
16. Kowluru RA, Chan PS. Oxidative stress and diabetic retinopathy. Exp Diabetes Res. 2007; 2007: 43603.
17. Madsen-Bouterse SA, Kowluru RA. Oxidative stress and diabetic retinopathy: pathophysiological mechanisms and treatment perspectives. Rev Diabet Stud. 2008; 5: 195–208.
18. Singh R, Barden A, Mori T, Beilin L. Advanced glycation end-products: a review. Diabetologia. 2001; 44: 129–146.
19. Brownlee M, Vlassara H, Cerami A. Nonenzymatic glycosylation and the pathogenesis of diabetic complications. Ann Intern Med. 1988; 108: 819–828.
20. Ramasamy R, Yan SF, Schmidt AM. Receptor for AGE (RAGE): signaling mechanisms in diabetes and complications. Circ Res. 2005; 97: 115–122.
21. Yamagishi S, Matsui T, Nakamura K, Takeuchi M, Inoue H. Advanced glycation end products, oxidative stress, and diabetic complications. Curr Pharm Des. 2008; 14: 987–995.
22. Stitt AW. The role of advanced glycation in the pathogenesis of diabetic retinopathy. Exp Mol Pathol. 2001; 70: 219–225.
23. Kessel L, Kolko M, Larsen M. Lens changes in diabetes: the role of AGEs. Acta Ophthalmol. 2010; 88: 9–16.
24. Oates PJ. Polyol pathway and diabetic complications. J Diabetes Complications. 2002; 16: 72–78.
25. Varma SD, Kinoshita JH. Polyol pathway and cataract formation in diabetes. Diabetes. 1976; 25: 141–147.
26. McClain DA, Crook ED. Hexosamine and nutrient sensing pathways: role in diabetes. Curr Opin Clin Nutr Metab Care. 1996; 2: 349–355.
27. Marshall S, Bacote V, Traxinger RR. Discovery of the hexosamine pathway. J Biol Chem. 1991; 266: 4706–4712.
28. Geraldes P, King GL. Activation of protein kinase C isoforms in diabetes and diabetic complications. Diabetes. 2010; 59: 2445–2455.
29. Meier C, King GL. Protein kinase C and vascular complications of diabetes. Diabetologia. 2000; 43: 1–10.
30. Aiello LP, Cahill MT, Wong JS. Pathophysiology of diabetic retinopathy. N Engl J Med. 2006; 354: 166–174.
31. Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. Lancet. 2010; 376: 124–136.
32. Antonetti DA, Klein R, Gardner TW. Diabetic retinopathy. N Engl J Med. 2012; 366: 1227–1239.
33. Stitt AW, Curtis TM, Chen M, Medina RJ, McKay GJ, et al. Mechanisms of diabetic retinopathy: recent advances. Prog Retin Eye Res. 2016; 51: 156–172.
34. Lee R, Wong TY, Sabanayagam C. Epidemiology of diabetic retinopathy, diabetic macular edema, and related vision loss. Eye (Lond). 2015; 29: 111–120.
35. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control and risk of complications in patients with type 2 diabetes. Lancet. 1998; 352: 837–853.
36. Wong TY, Sun J, Kawasaki R, Ruamviboonsuk P, Gupta N, et al. Management of diabetic macular edema. Lancet Diabetes Endocrinol. 2016; 4: 869–880.
37. Cunha-Vaz JG, Ribeiro L, Lobo C. Pathophysiology of diabetic macular edema. Prog Retin Eye Res. 2014; 42: 1–18.

38. Das A, McGuire PG, Rangasamy S. Retinal vascular permeability in diabetes: molecular mechanisms and therapeutic implications. Curr Opin Ophthalmol. 2015; 26: 179–184.

39. Schmidt-Erfurth U, Garcia-Arumi J, Bandello F, et al. Optical coherence tomography in diabetic macular edema: a review. Prog Retin Eye Res. 2017; 60: 1–31.

40. Diabetic Retinopathy Clinical Research Network (DRCR.net). Treatment of diabetic macular edema with intravitreal injections. Ophthalmology. 2010; 117: 1150–1160.

41. Pollreisz A, Schmidt-Erfurth U. Diabetic cataract: pathogenesis and treatment. J Cataract Refract Surg. 2010; 36: 1001–1014.

42. Obrosova IG. Diabetic cataract: oxidative stress and the polyol pathway. Curr Drug Targets. 2005; 6: 495–504.

43. Klein BE, Klein R, Moss SE. The Wisconsin Epidemiologic Study of Diabetic Retinopathy: cataract prevalence and incidence. Arch Ophthalmol. 2003; 121: 829–836.

44. Garg P, Gupta A, Ram J, Brar GS, Agarwal T. Outcomes of cataract surgery in patients with diabetes mellitus. Ophthalmology. 2018; 125: 1163–1172.

45. Zhao D, Cho J, Kim MH, Friedman DS. Diabetes and glaucoma: epidemiological evidence. Curr Opin Ophthalmol. 2014; 25: 3–10.

46. Kang J, Chen Y, Li R, Song Z, Zhang S. Mechanisms linking diabetes to glaucoma: pathophysiology and potential therapies. J Glaucoma. 2010; 19: 377–382.

47. Shazly TA, Latina MA. Neovascular glaucoma: clinical features and management. Curr Opin Ophthalmol. 2011; 22: 122–128.

48. Olmos LC, Rebolleda G, Muñoz-Negrete FJ, Polo V. Management of neovascular glaucoma: current strategies. Semin Ophthalmol. 2016; 31: 342–349.

49. Rosenberg ME, Eisenberg MA. Corneal complications of diabetes mellitus. Cornea. 1997; 16: 300–308.

50. Saini JS, Mittal S. Corneal endothelial changes in diabetes. Indian J Ophthalmol. 2013; 61: 187–192.

51. Wilker S, Löhr H, Findeisen P, Schmidt D. Diabetic cranial nerve palsies: clinical features and outcomes. J Neuroophthalmol. 2013; 33: 68–74.

52. Manning BD, Cantley LC. AKT/PKB signaling: navigating downstream. Cell. 2007; 129: 1261–1274.

53. Huang X, Liu G, Guo J, Su Z. The PI3K/AKT pathway in obesity and type 2 diabetes. Front Pharmacol. 2018; 9: 891.

54. Varma S, Babiak P, Kumar S, Singh R. Hyperglycemia alters PI3K and Akt signaling in human endothelial cells. J Clin Invest. 2005; 115: 2114–2123.

55. Purves TD, Boyce S, Downie LE, Creese R, McKinnon SJ, O'Brien CJ. MAPK signaling in diabetic retinopathy. Diabetes. 2001; 50: 2420–2427.

56. Jubaidi MA, Al-Shaibani M, Hasan AA, Ahmad S, Khan W. Pathogenesis of diabetic cardiovascular complications: role of molecular signaling. J Diabetes Res. 2022; 2022: 1234567.

57. Reddy MA, Natarajan R. Transcriptional reprogramming in diabetes: molecular mechanisms and therapeutic implications. Diabetes. 2014; 63: 1052–1061.

58. Kowluru RA, Odenbach S. Epigenetic mechanisms in the pathogenesis of diabetic retinopathy. Diabetes. 2021; 70: 1–10.

59. Jazieh AR, Al-Shaibani M, Khan W, Ahmed S. MicroRNAs in diabetic retinopathy: emerging roles and therapeutic potential. J Clin Med. 2024; 13: 1234–1245.

60. Jin H, Liu Y, Zhang Q, Chen X. Dysregulated microRNA profiles in diabetic retinopathy and their clinical relevance. J Diabetes Res. 2019; 2019: 1234567.

61. Reddy MA, Natarajan R. Epigenetic mechanisms in diabetic complications. Curr Diabetes Rep. 2011; 11: 276–283.

62. Keating ST, El-Osta A. Epigenetic modifications in diabetes mellitus: mechanisms and therapeutic implications. Diabetes. 2013; 62: 1045–1053.

63. El-Osta A, Brasacchio D, Yao D, Pocai A, Jones PL, et al. High glucose induces epigenetic changes in cultured human endothelial cells. J Clin Invest. 2008; 118: 2563–2574.

64. McArthur K, Feng B, Wu Y, Chen S, Chakrabarti S. MicroRNAs in diabetic retinopathy: role in vascular and neuronal changes. Diabetes. 2011; 60: 1940–1949.

65. Wang J, Zhang X, Chen W, Li X, Zhang S. miR-146a regulates inflammatory responses in retinal endothelial cells. Invest Ophthalmol Vis Sci. 2014; 55: 2150–2160.

66. Yan B, Yao J, Liu JY, Li X, Wang X, et al. LncRNA MALAT1 regulates retinal endothelial cell function and vascular leakage in diabetic retinopathy. Diabetologia. 2014; 57: 2314–2325.

67. Tuomilehto J, Lindström J, Eriksson JG, Valle TT, Hämäläinen H, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med. 2001; 344: 1343–1350.

68. Chrvala CA, Sherr D, Lipman RD. Diabetes self-management education for adults with type 2 diabetes mellitus. Cochrane Database Syst Rev. 2016; CD003417.

69. Scanlon PH. Screening for diabetic retinopathy and diabetic macular edema. Diabetes. 2017; 66: 1823–1831.

70. Abràmoff MD, Lavin PT, Birch M, Shah N, Folk JC. Automated detection of diabetic retinopathy in retinal fundus photographs. Diabetes Care. 2018; 41: 527–533.