Diabetes Complications: An Updated Review for Dentist, Optometrist, Radiologists, Nursing, Laboratory Professionals, and Other Healthcare Professionals

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Abstract

Background: Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia and progressive multi-organ injury affecting vascular, neural, renal, and retinal systems. The global burden continues to rise rapidly, creating substantial clinical and economic challenges. Diabetic complications arise from interconnected macrovascular and microvascular dysfunction driven by metabolic, inflammatory, and epigenetic mechanisms.

Aim: This review aims to synthesize current evidence on the molecular mechanisms, organ crosstalk, and clinical manifestations of diabetes-related complications, with emphasis on renal, cardiovascular, neurological, and retinal involvement. It also highlights emerging therapeutic strategies relevant to multidisciplinary healthcare professionals.

Methods: A narrative review approach was used, integrating findings from recent experimental studies, clinical investigations, single-cell RNA sequencing, and multiomics analyses. Evidence was critically examined to map shared pathogenic pathways across diabetic complications.

Results: Diabetic complications are mediated by hyperglycemia-induced oxidative stress, mitochondrial dysfunction, endoplasmic reticulum stress, chronic inflammation, and accumulation of advanced glycation end products. These processes disrupt endothelial function and activate inflammatory cascades such as NF-κB and NLRP3 inflammasome signaling. Organ-specific manifestations include diabetic kidney disease with podocyte loss and fibrosis, cardiovascular disease driven by endothelial-to-mesenchymal transition and atherosclerosis, neurodegeneration linked to blood–brain barrier dysfunction and mitochondrial injury, and diabetic retinopathy characterized by retinal vascular damage, ferroptosis, and pathological angiogenesis. Metabolic memory and epigenetic modifications sustain disease progression even after glycemic control.

Conclusion: Diabetic complications represent a unified systemic disorder rather than isolated organ diseases. Integrated molecular pathways drive progressive multi-organ dysfunction, supporting the need for early intervention and multi-target therapeutic strategies.

Keywords: Diabetes mellitus, microvascular complications, macrovascular disease, endothelial dysfunction, oxidative stress, epigenetics, organ crosstalk

Introduction

Diabetes mellitus (DM) encompasses a heterogeneous group of chronic metabolic disorders primarily defined by persistent hyperglycemia, resulting from either absolute insulin deficiency, relative insulin insufficiency, impaired insulin receptor activity, or a combination of these pathophysiological mechanisms. The disease represents a major and escalating global public health concern, with a substantial and continuously increasing burden on healthcare systems worldwide. Epidemiological data indicate that in 2022, approximately 828 million adults were living with diabetes globally, reflecting a dramatic increase of around 630 million cases compared with 1990. This corresponds to a prevalence rate of 13.9% among women and 14.3% among men, demonstrating a nearly comparable distribution across sexes. Projections suggest that this figure will exceed 1.31 billion individuals by 2050, highlighting the progressive and expanding nature of the disease burden and its profound implications for global health economics and healthcare infrastructure [2][3][4]. Despite the rapid rise in diabetes prevalence, the expansion of effective treatment

coverage has not progressed at a comparable rate. This disparity is particularly evident in low- and middle-income countries, where healthcare access limitations, resource constraints, and insufficient screening programs contribute to significant gaps in disease management. Current evidence indicates that approximately 59% of individuals with diabetes worldwide, particularly those aged 30 years and above, remain untreated. This treatment gap represents a critical challenge in global diabetes control strategies and underscores the need for strengthened healthcare delivery systems, improved accessibility to pharmacological interventions, and enhanced public health policies aimed at early detection and sustained disease management [2]. From a pathophysiological perspective, chronic hyperglycemia is associated with widespread metabolic dysregulation that contributes to both macrovascular and microvascular complications. These pathological processes affect multiple organ systems, including the cardiovascular, cerebral, renal, and peripheral vascular networks. The cumulative burden of these vascular complications is increasingly conceptualized under the term "diabetic panvascular disease (DPD)," which reflects the shared molecular pathways and interconnected risk factors underlying the diverse manifestations of diabetic vascular injury. This conceptual framework emphasizes the systemic nature of diabetes-related complications rather than isolated organ-specific disease processes [5].

Recent scientific investigations have further highlighted the complex interplay between systemic metabolic disturbances and localized tissue-specific factors that either exacerbate or mitigate the progression of diabetic complications. These studies suggest that the development of end-organ damage in diabetes is not solely determined by glycemic control but also influenced by inflammatory mediators, oxidative stress, genetic predisposition, and protective compensatory mechanisms within affected tissues. This evolving understanding has shifted research focus toward integrated multi-organ perspectives in disease progression and management [6]. Accordingly, contemporary literature increasingly advocates for a comprehensive approach to diabetic complication management, integrating molecular insights with clinical prevention strategies and multi-organ therapeutic interventions. Such an approach is essential for addressing the multifactorial nature of diabetes mellitus and its systemic complications. By consolidating current evidence on underlying mechanisms, preventive strategies, and emerging therapeutic modalities, this framework provides a robust foundation for improving long-term patient outcomes and reducing the global burden of diabetic disease.

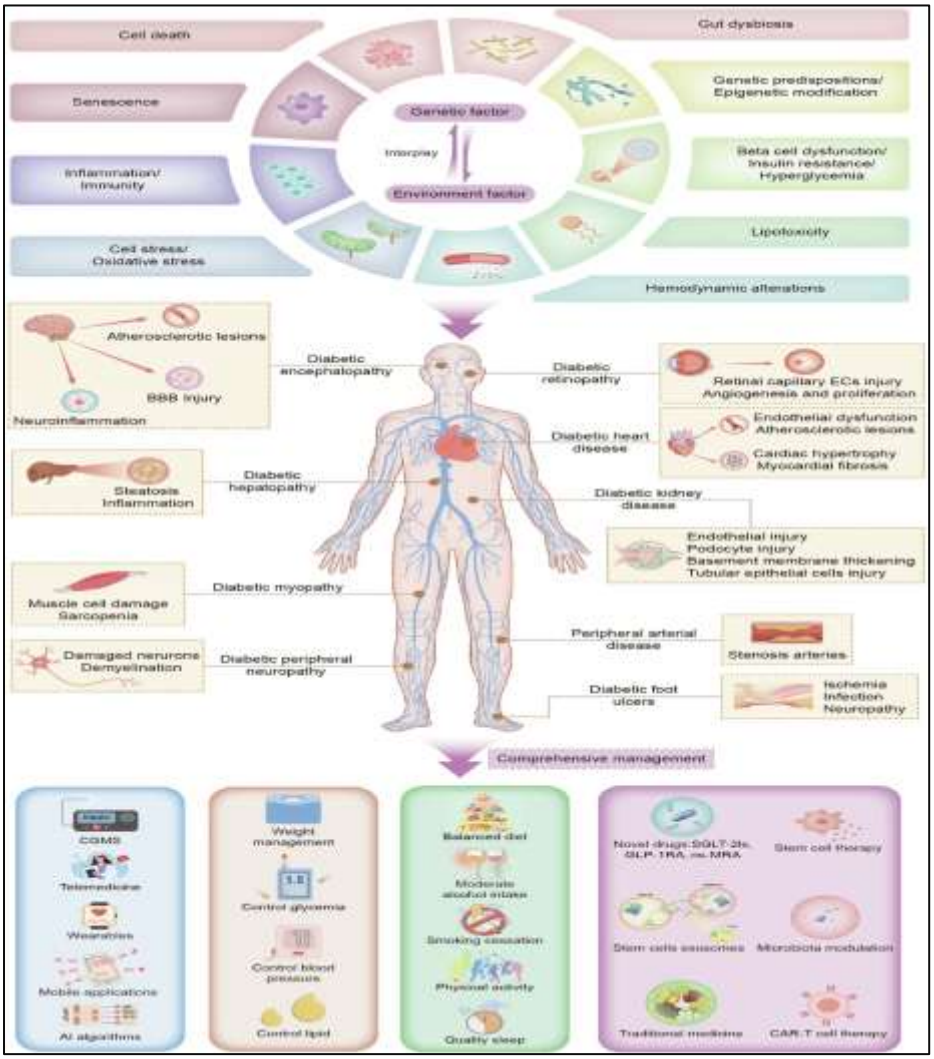

Fig. 1: Diabetes and Its complications.

Molecular mechanisms and mediators of organ crosstalk in diabetic complications

Diabetes mellitus encompasses a spectrum of metabolic disorders that include type 1 diabetes mellitus (T1D), an autoimmune condition typically presenting in early life; type 2 diabetes mellitus (T2D), a predominantly non-autoimmune, adult-onset disorder accounting for more than 90% of global cases; and less common forms such as monogenic diabetes, including Maturity-Onset Diabetes of the Young resulting from single-gene mutations, neonatal diabetes, gestational diabetes associated with pregnancy, and latent autoimmune diabetes in adults (LADA), which presents with autoimmune features later in life. The pathogenesis of diabetes is multifactorial, arising from complex interactions between genetic susceptibility and environmental influences. Among these, T2D represents the dominant clinical burden, accounting for approximately 96% of all cases, and is therefore the primary focus of current mechanistic and therapeutic research into diabetic complications and systemic organ dysfunction [7][8][9][10]. At the core of diabetic pathophysiology lies pancreatic β-cell dysfunction, which serves as a central regulatory node in glucose homeostasis and the development of chronic hyperglycemia. In type 2 diabetes, impaired insulin secretion is closely associated with peripheral insulin resistance in key metabolic tissues such as the liver and skeletal muscle. This dual defect contributes to progressive metabolic imbalance and sustained hyperglycemic states. Advances in molecular biology have highlighted the therapeutic potential of gene-editing technologies, particularly CRISPR-Cas9, in enabling the precise differentiation of stem cells into functional β-cells. In addition, modulation of non-coding RNAs such as lncRNA MIR503HG, as well as regulation of zinc transporter proteins like ZnT8 in stem cell-derived pancreatic progenitors, has demonstrated improvements in insulin synthesis and secretion. These findings suggest that stem cell-based regenerative strategies combined with gene-editing approaches may represent a future direction for diabetes treatment, although long-term safety, stability, and functional durability remain under investigation [11][12][13][14][15].

Beyond β-cell dysfunction, diabetes pathogenesis is driven by a cluster of interconnected metabolic abnormalities collectively referred to as the "ominous octet." This includes lipotoxicity, impaired incretin signaling, hyperglucagonemia, increased renal glucose reabsorption, and central insulin resistance, all of which contribute to progressive hyperglycemia and systemic metabolic deterioration. The development of diabetic complications is further mediated by overlapping pathological mechanisms, including persistent hyperglycemia, dyslipidemia, hemodynamic stress, oxidative stress, accumulation of advanced glycation end products (AGEs), and chronic low-grade inflammation. These processes collectively disrupt cellular homeostasis and promote progressive tissue injury across multiple organ systems [16][5][17]. Endothelial cells play a central role in mediating vascular injury in diabetes due to their insulin-independent glucose uptake via glucose transporters such as GLUT1, GLUT2, and GLUT3. This results in intracellular glucose overload, which disrupts mitochondrial oxidative phosphorylation, impairs fatty acid metabolism, and alters key intracellular signaling pathways responsible for maintaining cellular integrity, metabolic adaptation, and immune regulation. Hyperglycemia-induced metabolic reprogramming leads to a shift from oxidative phosphorylation toward glycolysis, a process that increases the generation of reactive oxygen species (ROS) and other toxic metabolic byproducts. These changes contribute significantly to endothelial dysfunction and vascular pathology [18][19][20][21][22].

Furthermore, endoplasmic reticulum (ER) stress and mitochondrial dysfunction are closely interconnected through mitochondria-associated ER membranes, where disruption of calcium homeostasis leads to mitochondrial fragmentation, oxidative stress amplification, and activation of apoptotic pathways. This organelle-level dysfunction plays a critical role in progressive cellular injury observed in diabetic complications. Concurrently, chronic hyperglycemia activates innate immune pathways, particularly the nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) inflammasome, which promotes the release of pro-inflammatory cytokines. This sustained inflammatory response contributes to immune cell dysfunction, vascular injury, immune senescence, and progressive target organ damage [23][24][25][26][27][28][29][30]. Another important mediator in diabetic organ crosstalk is endothelin-1 (ET-1), a potent vasoactive peptide that contributes to vasoconstriction, inflammation, hypertrophy, and fibrosis within cardiovascular, renal, and vascular tissues. ET-1 exerts its effects primarily through endothelin type A receptors (ETARs) located on vascular smooth muscle cells, where it promotes vasoconstriction, cellular proliferation, and inflammatory signaling. In contrast, endothelin type B receptors (ETBRs), predominantly expressed on endothelial cells, mediate vasodilation through the release of nitric oxide and prostacyclin, thereby providing a counter-regulatory mechanism. However, in diabetic conditions, the balance between these receptor-mediated pathways is often disrupted, favoring pro-inflammatory and vasoconstrictive effects. Collectively, these molecular mechanisms contribute to endothelial injury, fibrosis, tissue remodeling, and progressive multi-organ dysfunction, highlighting the interconnected nature of diabetic complications across organ systems [31][32].

Diabetic kidney disease

Diabetic kidney disease (DKD) represents one of the most significant microvascular complications of diabetes mellitus and is a major determinant of long-term morbidity and mortality. Diabetic vasculopathy is broadly categorized into macroangiopathy and microangiopathy, with the latter being a defining feature of chronic hyperglycemia. Persistent elevation of blood glucose levels leads to structural and functional alterations in the vascular endothelium, including endothelial dysfunction and progressive thickening of the vascular basement membrane. These pathological changes constitute the hallmark of diabetic microangiopathy and contribute directly to the progressive deterioration of renal function observed in DKD. Epidemiological data indicate that approximately 22–40% of individuals with diabetes

develop DKD, making it the leading cause of end-stage kidney disease worldwide, often necessitating renal replacement therapies such as dialysis or kidney transplantation, thereby posing a substantial burden on global healthcare systems [5][33][34]. The pathogenesis of DKD is multifactorial and involves a complex interaction of hemodynamic abnormalities, metabolic dysregulation, inflammatory signaling, fibrotic remodeling, and epigenetic modifications. One of the earliest detectable alterations in DKD is intraglomerular hyperfiltration at the level of individual nephrons. This hyperfiltration state is primarily driven by systemic hyperglycemia and enhanced angiotensin II activity, which arises through dysregulated tubuloglomerular feedback mechanisms. These hemodynamic changes result in increased glomerular capillary pressure and excessive filtration load, initiating early renal injury and functional stress within the nephron unit [10][35][36].

Advanced molecular investigations, including single-cell RNA sequencing of kidney biopsy samples from patients with type 2 diabetes-associated DKD, have identified a distinct hyperfiltration-associated gene expression signature comprising approximately 1,240 genes. This transcriptomic profile highlights significant endothelial stress and reveals intricate cellular interactions between endothelial and mesangial cells, emphasizing the importance of intercellular communication in disease progression. The sustained hemodynamic stress imposed by hyperfiltration leads to increased intraglomerular wall tension and shear stress, particularly affecting podocytes, which are highly specialized epithelial cells critical for maintaining glomerular filtration barrier integrity. In addition, tubular epithelial cells experience increased oxygen demand to support enhanced reabsorptive activity, further contributing to local hypoxic stress within renal tissues [37][36]. At the intracellular level, calcium signaling plays a pivotal role in mediating mechanical stress responses within renal cells. Calcium influx regulated by transient receptor potential channels influences the activation of Rho and Rac GTPase signaling pathways, which are central to cytoskeletal organization and cellular structural adaptation. These pathways converge on mechanotransduction signaling networks, including the Yes-associated protein/transcriptional coactivator with PDZ-binding motif (YAP/TAZ) pathway, which is activated in response to mechanical stretch and stress. Activation of these signaling cascades promotes reorganization of the actin cytoskeleton in podocytes, thereby altering cell shape, stability, and filtration function [38].

In parallel, mammalian target of rapamycin complex 1 (mTORC1) signaling is activated in response to growth factors and insulin signaling in diabetic conditions, leading to podocyte hypertrophy. While initially adaptive, sustained mTORC1 activation increases cellular metabolic demand and renders podocytes more susceptible to injury and dysfunction. The combined effects of mechanical stress, metabolic overload, and signaling dysregulation ultimately lead to progressive podocyte injury, mesangial cell expansion, and thickening of the glomerular basement membrane. These structural abnormalities evolve into glomerulosclerosis and tubulointerstitial fibrosis, which represent advanced and often irreversible stages of DKD [39][40]. Collectively, DKD arises from a tightly interconnected network of hemodynamic stress, metabolic disturbance, and molecular signaling dysregulation. The progression from early hyperfiltration to chronic fibrosis reflects continuous cross-talk between vascular, glomerular, and tubular compartments, underscoring the systemic nature of diabetic renal injury and the complexity of its pathophysiological mechanisms.

Diabetic kidney disease (DKD) develops through interconnected structural, metabolic, inflammatory, and epigenetic mechanisms that progressively damage both glomerular and tubular compartments of the kidney. Early disease is characterized by metabolic reprogramming in podocytes, where oxidative stress triggers apoptosis and functional decline. Podocyte-specific genetic alterations, such as Abca1 deletion, lead to mitochondrial dysfunction driven by cardiolipin abnormalities, increasing susceptibility to DKD. In addition, lipid accumulation in the form of cholesterol-rich droplets, combined with persistent hyperglycemia and impaired insulin signaling, accelerates podocyte injury, detachment, and loss. Since podocytes are essential for maintaining the glomerular filtration barrier, their depletion is a central driver of glomerulosclerosis, a defining feature of DKD progression [41][42][43][44]. Oxidative stress, advanced glycation end products, and chronic inflammation further promote glomerular cell senescence through dysregulation of the GSK3β–Nrf2 signaling pathway. This impairs cellular repair capacity and intensifies inflammatory and fibrotic responses within renal tissue. Pharmacological agents such as metformin, dapagliflozin, and GLP-1 receptor agonists have demonstrated protective effects by reducing cellular senescence and improving metabolic balance in DKD. Additionally, epigenetic and DNA repair mechanisms involving genes such as NEPH1 and RCAN1 contribute to restoration of the slit diaphragm, highlighting the importance of genomic stability in podocyte survival [45][46][47][48][49].

A key pathological feature of DKD is disrupted crosstalk between podocytes and endothelial cells. Alterations in angiogenic signaling, including reduced angiopoietin-1 to angiopoietin-2 ratios, abnormal vascular endothelial growth factor (VEGF) expression, and endothelin-1 dysregulation, contribute to endothelial dysfunction, abnormal angiogenesis, and impaired vascular integrity. These changes also disrupt lymphangiogenesis, leading to interstitial edema and fibrosis. Together, these vascular abnormalities amplify renal injury and promote progressive loss of kidney function [50][51][52]. Recent research has shifted DKD understanding from a glomerulus-centered model to one emphasizing proximal tubular injury. Tubular epithelial cells undergo metabolic stress due to hyperglycemia, resulting in hypertrophy, energy imbalance, ATP depletion, and hypoxia. This process is accompanied by activation of AMPK signaling and maladaptive metabolic reprogramming. Defects in fatty acid oxidation, driven by suppression of key transcription factors such as SREBP and PPAR-γ, further exacerbate mitochondrial dysfunction and energy failure. The release of mitochondrial DNA and RNA activates inflammatory pathways involving interferon regulatory factors and TGF-β signaling, ultimately promoting immune cell recruitment and fibrotic remodeling [53][54][55][56][57].

Innate immune activation is a central driver of DKD progression. Toll-like receptor signaling and complement system activation trigger NF-κB–mediated inflammation, apoptosis, and fibrosis. The NLRP3 inflammasome further amplifies inflammation through IL-1β and IL-18 release, sustaining immune cell infiltration by macrophages and T cells. Complement components such as C3 and C5 generate potent anaphylatoxins that enhance endothelial-to-mesenchymal transition and activate ROS and PKC-dependent injury pathways. These immune mechanisms create a self-perpetuating cycle of inflammation and renal damage. Anti-inflammatory strategies are increasingly considered central to future DKD therapy [58][59][60][61][62][63][64][65][66][67][68][69][70][71]. Another critical concept in DKD is "metabolic memory," which describes the persistence of molecular damage even after glycemic control is achieved. Early hyperglycemic exposure induces long-lasting epigenetic changes, including DNA methylation, histone modifications, and persistent activation of signaling pathways such as NF-κB, PKC, and TGF-β. These changes maintain inflammatory and fibrotic activity despite later normalization of blood glucose levels. Podocyte DNA damage and altered methylation patterns correlate with declining glomerular filtration rate, while macrophage epigenetic reprogramming influences inflammatory polarization and metabolic activity. These findings emphasize that DKD progression is not solely dependent on current glycemic status but also on prior metabolic exposure [72][73][74][75]. Overall, DKD is a multifactorial disease involving glomerular hyperfiltration, podocyte loss, tubular metabolic injury, immune activation, and epigenetic imprinting. Emerging therapeutic strategies targeting inflammation, metabolic pathways, and epigenetic regulation offer promising directions for slowing or reversing disease progression and improving long-term renal outcomes.

Cardiovascular Complications:

Diabetes-related cardiovascular disease (CVD) represents the leading cause of mortality among individuals with both type 1 and type 2 diabetes, accounting for approximately 44% and 52% of deaths respectively. The cardiovascular complications of diabetes include a broad spectrum of macrovascular and microvascular disorders, primarily coronary artery disease (CAD), diabetic cardiomyopathy (DCM), cerebrovascular disease, peripheral artery disease (PAD), and diabetic encephalopathy. These conditions arise from interconnected mechanisms involving endothelial dysfunction, oxidative stress, chronic inflammation, mitochondrial injury, and endoplasmic reticulum stress, all of which form a complex pathological network that drives progressive vascular and cardiac damage [76]. Coronary artery disease in diabetes is characterized by diffuse and segmental atherosclerotic lesions affecting multiple vascular territories, reflecting systemic macrovascular involvement. A central early event in diabetic cardiovascular pathology is endothelial dysfunction, which serves as both an initiator and amplifier of vascular injury. Hyperglycemia reduces nitric oxide bioavailability, increases oxidative stress, and activates inflammatory signaling pathways, leading to impaired vascular relaxation and endothelial damage. A key concept in disease persistence is "metabolic memory," where prior hyperglycemic exposure induces long-lasting epigenetic and molecular alterations in endothelial cells. These include activation of NF-κB signaling, dysregulation of microRNAs such as miR-27a-3p and miR-29, suppression of Nrf2, activation of TGF-β pathways, and induction of endothelial-to-mesenchymal transition (EndMT). These persistent changes continue even after glycemic normalization and contribute to fibrosis, vascular stiffness, and cardiac dysfunction [80][81][82].

EndMT plays a crucial role in diabetic atherosclerosis, driven by hyperglycemia, advanced glycation end products (AGEs), and oxidized low-density lipoprotein (ox-LDL). These stimuli activate proinflammatory pathways, increase oxidative stress, and promote phenotypic transformation of endothelial cells into mesenchymal-like cells. This is reflected by increased expression of mesenchymal markers such as α-SMA and fibronectin and decreased endothelial markers such as CD31. The AGE–RAGE axis further amplifies NF-κB-mediated inflammatory cytokine production, worsening endothelial dysfunction. Additionally, disruption of the CAV1–CAVIN1–LC3B axis impairs autophagy and enhances LDL transcytosis, accelerating plaque formation. Ox-LDL further promotes EndMT via TGF-β activation and ROS production, contributing to plaque instability and vascular injury. Multiomics and single-cell RNA sequencing studies have identified novel EndMT-associated genes and transcriptional regulators, highlighting cellular heterogeneity and complex regulatory networks in atherosclerotic lesions [83][84][85][86][87][88]. Mitochondrial dysfunction is another central contributor to diabetic vascular disease. Hyperglycemia increases mitochondrial reactive oxygen species (ROS), leading to oxidative damage of mitochondrial DNA and impaired energy metabolism. This triggers dysregulated mitophagy through SIRT1 and PINK1/Parkin pathways, further worsening endothelial injury and vascular dysfunction. These findings identify mitochondria as potential therapeutic targets in diabetic atherosclerosis [89][90].

Diabetic cardiomyopathy (DCM) is defined as myocardial dysfunction independent of coronary artery disease or hypertension. A key pathological mechanism involves the accumulation of AGEs, which crosslink extracellular matrix proteins, inhibit matrix degradation, and increase myocardial stiffness, resulting in diastolic dysfunction. This mechanical stress activates profibrotic signaling pathways mediated by TGF-β, TNF, angiotensin II, and interleukins. Transcriptomic studies have identified multiple fibroblast subpopulations, including disease-associated clusters that expand significantly in diabetic myocardium. Mitochondrial ROS accumulation activates the NLRP3 inflammasome, promoting pyroptosis and worsening myocardial injury. Clinically, DCM progresses from subclinical diastolic dysfunction to heart failure with preserved ejection fraction (HFpEF), which is highly prevalent in type 2 diabetes, and eventually to systolic heart failure with reduced ejection fraction. Impaired calcium handling, insulin resistance, and metabolic abnormalities such as elevated free fatty acids further contribute to disease progression

[91][92][93][94][95][96][97][98][99][100][101][102][103][104]. Diabetes also contributes to diabetic encephalopathy, which includes ischemic stroke, vascular dementia, and neurodegenerative disorders characterized by cognitive decline and memory impairment. Hyperglycemia disrupts neuronal signaling pathways, including ErbB4 and mTOR, leading to tau protein hyperphosphorylation and impaired autophagy. Blood–brain barrier dysfunction, driven by oxidative stress and inflammation, further impairs neuronal homeostasis. Mitochondrial dysfunction reduces amyloid clearance, while endoplasmic reticulum stress activates NF-κB-mediated neuroinflammation. Additionally, disrupted iron metabolism contributes to neurotoxicity and cognitive decline, with iron-chelating agents such as desferrioxamine emerging as potential therapeutic options [105][106][107][108][109][110][111][112][113].

Peripheral artery disease in diabetes is characterized by distal arterial stenosis affecting below-the-knee vessels, contrasting with proximal disease patterns in non-diabetic individuals. This distal involvement reduces collateral circulation and limits revascularization options. Hyperglycemia promotes vascular calcification through AGE accumulation, leading to hydroxyapatite deposition in arterial walls and contributing to severe ischemic complications such as intermittent claudication and limb ischemia [114][115][116][117]. Overall, diabetes-related cardiovascular disease results from a convergence of endothelial dysfunction, oxidative stress, inflammation, mitochondrial damage, and metabolic dysregulation. Future therapeutic strategies increasingly focus on precision medicine approaches, multiomics integration, and mitochondrial-targeted interventions to improve prevention and treatment outcomes in diabetic cardiovascular complications.

Diabetic retinopathy (DR)

Diabetic retinopathy (DR) is one of the most prevalent microvascular complications of diabetes mellitus and represents a leading cause of preventable blindness worldwide. It affects approximately 34.6% of individuals with diabetes, highlighting its substantial clinical and public health burden. The pathogenesis of DR is highly complex and involves interrelated vascular, neuronal, inflammatory, and metabolic mechanisms. Emerging evidence emphasizes the role of premature cellular senescence within retinal tissues, accompanied by the persistent secretion of pro-inflammatory cytokines. These senescent cells propagate a paracrine senescence effect, amplifying local inflammation and promoting pathological angiogenesis, thereby accelerating disease progression and retinal damage [118][119][120][121]. Chronic hyperglycemia is a central driver of retinal vascular injury, particularly targeting endothelial cells (ECs), which are critical for maintaining retinal microvascular integrity. Elevated glucose levels disrupt endothelial cell–cell junctions, induce apoptosis, and lead to the formation of acellular capillaries, contributing to breakdown of the inner blood–retinal barrier. These early structural changes compromise retinal homeostasis and facilitate leakage, edema, and ischemia. Hyperglycemia further induces extensive metabolic reprogramming within endothelial cells, characterized by activation of the polyol, hexosamine, and protein kinase C (PKC) pathways, as well as accumulation of advanced glycation end products (AGEs). These metabolic disturbances increase oxidative stress, sustain chronic inflammation, and promote premature endothelial senescence, all of which contribute to progressive retinal dysfunction [22][122].

Recent research has identified ferroptosis as a novel and significant mechanism of retinal endothelial cell death in DR. Ferroptosis is an iron-dependent, lipid peroxidation-driven form of regulated cell death that contributes to vascular injury in the retina. In this context, TRIM46-mediated ferroptosis has been shown to promote degradation of glutathione peroxidase 4 (GPX4), a key antioxidant enzyme, thereby exacerbating oxidative damage and disrupting iron homeostasis. In addition to ferroptosis, multiple other forms of programmed cell death, including apoptosis, necroptosis, pyroptosis, and parthanatos, collectively contribute to retinal endothelial cell loss, further amplifying vascular instability and disease severity [123][124][125][126][127][128]. Advances in multiomics technologies and artificial intelligence have significantly enhanced the understanding of DR at the cellular and molecular levels. High-throughput analyses have revealed metabolic reprogramming in retinal microglia, characterized by a shift toward glycolytic metabolism and reduced tricarboxylic acid cycle activity under diabetic conditions. A distinct subpopulation of microglia with immune-regulatory properties has also been identified, exhibiting activation of MAPK, JAK/STAT, and IL-17 signaling pathways. These findings highlight the heterogeneity of retinal immune responses in diabetes and their role in disease progression [129][130][131][132].

A critical aspect of DR pathogenesis is the interaction between microglia and endothelial cells. Under hyperglycemic conditions, endothelial cells release colony-stimulating factor 1, which activates microglia through CSF1R-dependent MAPK signaling pathways, thereby promoting inflammation and angiogenesis. Additionally, necroptotic microglia expressing RIP3 and MLKL contribute to pathological neovascularization by secreting fibroblast growth factor 2, which stimulates endothelial proliferation. Neutrophil extracellular traps further aggravate retinal injury by inducing oxidative stress, endothelial apoptosis, and breakdown of the blood–retinal barrier, reinforcing vascular dysfunction and inflammatory damage [132][134][135]. High-throughput gene expression profiling and single-cell RNA sequencing have identified key molecular mediators of DR, including insulin-like growth factor 1 (IGF-1) and secreted phosphoprotein 1 (Spp1), which are predominantly expressed by microglia and associated with increased production of pro-inflammatory cytokines such as IL-1β and TNF. Elevated vitreous levels of these mediators in DR patients further confirm their clinical relevance. In advanced stages of the disease, pathological neovascularization driven by vascular endothelial growth factor (VEGF) and hypoxia-induced signaling results in fragile, immature vessels prone to hemorrhage and retinal detachment. Identification of downstream mediators such as G protein subunit alpha i2 (Gαi2) highlights additional targets involved in VEGF-driven angiogenic signaling and retinal vascular remodeling

[131][136][137][138][139]. Overall, diabetic retinopathy is driven by a multifactorial interplay of endothelial dysfunction, metabolic reprogramming, immune activation, ferroptosis, and microglia–endothelial cell crosstalk. Integrating multiomics approaches with advanced molecular profiling has significantly improved the understanding of its pathogenesis. These insights provide a strong foundation for developing targeted therapeutic strategies aimed at regulating inflammation, preventing endothelial cell loss, and inhibiting pathological angiogenesis to reduce vision loss in diabetic patients.

Conclusion

Diabetes-related complications arise from shared molecular and cellular mechanisms that extend across multiple organ systems. Chronic hyperglycemia initiates endothelial injury, mitochondrial dysfunction, oxidative stress, and persistent inflammatory activation, which collectively drive progressive tissue damage. These processes are reinforced by metabolic memory and epigenetic changes that sustain disease activity even after glucose normalization. As a result, diabetic kidney disease, cardiovascular disease, retinopathy, and encephalopathy develop through overlapping pathways involving vascular dysfunction, immune dysregulation, and fibrotic remodeling. Current evidence shifts the understanding of diabetes from isolated organ pathology to an integrated systemic disease. This perspective highlights the importance of early detection, strict metabolic control, and targeted therapies addressing inflammation, oxidative stress, and epigenetic regulation. Emerging approaches using multiomics profiling and precision medicine offer promising opportunities to identify high-risk patients and develop individualized treatment strategies. Effective management of diabetes complications requires coordinated multidisciplinary care supported by molecular insights and early intervention strategies aimed at preventing irreversible organ damage.

References

1. American Diabetes, A. Diagnosis and classification of diabetes mellitus. *Diabetes Care* **34**, S62–S69 (2011).
2. Collaboration, N. C. D. R. F. Worldwide trends in diabetes prevalence and treatment from 1990 to 2022: a pooled analysis of 1108 population-representative studies with 141 million participants. *Lancet* **404**, 2077–2093 (2024).
3. Collaborators, G. B. D. D. Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet* **402**, 203–234 (2023).
4. Chan, J. C. N. et al. The *Lancet* Commission on diabetes: using data to transform diabetes care and patient lives. *Lancet* **396**, 2019–2082 (2021).
5. Zhang, X., Zhang, J., Ren, Y., Sun, R. & Zhai, X. Unveiling the pathogenesis and therapeutic approaches for diabetic nephropathy: insights from panvascular diseases. *Front Endocrinol.***15**, 1368481 (2024).
6. Yu, M. G. et al. Protective factors and the pathogenesis of complications in diabetes. *Endocr. Rev.* **45**, 227–252 (2024).
7. Jia, W. et al. Standards of medical care for type 2 diabetes in China 2019. *Diabetes Metab. Res Rev.* **35**, e3158 (2019).
8. American Diabetes Association Professional Practice Diagnosis and classification of diabetes: standards of care in diabetes-2024. *Diabetes Care* **47**, S20–S42 (2024).
9. Cole, J. B. & Florez, J. C. Genetics of diabetes mellitus and diabetes complications. *Nat. Rev. Nephrol.* **16**, 377–390 (2020).
10. Abel, E. D. et al. Diabetes mellitus-Progress and opportunities in the evolving epidemic. *Cell* **187**, 3789–3820 (2024).
11. Hsu, P. D., Lander, E. S. & Zhang, F. Development and applications of CRISPR-Cas9 for genome engineering. *Cell* **157**, 1262–1278 (2014).
12. Gerace, D. et al. CRISPR-targeted genome editing of mesenchymal stem cell-derived therapies for type 1 diabetes: a path to clinical success?. *Stem Cell Res Ther.* **8**, 62 (2017).
13. El Nahas, R., Al-Aghbar, M. A., Herrero, L., van Panhuys, N. & Espino-Guarch, M. Applications of genome-editing technologies for type 1 diabetes. *Int. J. Mol. Sci*. **25**, (2023).
14. Xu, Y. et al. LINC MIR503HG Controls SC-beta Cell differentiation and insulin production by targeting CDH1 and HES1. *Adv. Sci.* **11**, e2305631 (2024).
15. Ma, Q. et al. ZnT8 loss-of-function accelerates functional maturation of hESC-derived beta cells and resists metabolic stress in diabetes. *Nat. Commun.* **13**, 4142 (2022).
16. Defronzo, R. A. Banting Lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes* **58**, 773–795 (2009).
17. Forbes, J. M. & Cooper, M. E. Mechanisms of diabetic complications. *Physiol. Rev.* **93**, 137–188 (2013).
18. Yazdani, S. et al. Dynamic glucose uptake, storage, and release by human microvascular endothelial cells. *Mol. Biol. Cell* **33**, ar106 (2022).
19. Zhang, Z. Y. et al. Molecular mechanisms of glucose fluctuations on diabetic complications. *Front Endocrinol.***10**, 640 (2019).
20. Srivastava, S. P. et al. Endothelial SIRT3 regulates myofibroblast metabolic shifts in diabetic kidneys. *iScience* **24**, 102390 (2021).
21. Hou, Y. et al. Mitochondrial oxidative damage reprograms lipid metabolism of renal tubular epithelial cells in the diabetic kidney. *Cell Mol. Life Sci.* **81**, 23 (2024).
22. Liao, Y. L., Fang, Y. F., Sun, J. X. & Dou, G. R. Senescent endothelial cells: a potential target for diabetic retinopathy. *Angiogenesis* **27**, 663–679 (2024).

23. Liu, Y. et al. Mitochondria-associated endoplasmic reticulum membrane (MAM): a dark horse for diabetic cardiomyopathy treatment. *Cell Death Discov.* **10**, 148 (2024).
24. Zhang, Y. et al. Synergistic mechanism between the endoplasmic reticulum and mitochondria and their crosstalk with other organelles. *Cell Death Discov.* **9**, 51 (2023).
25. Zhao, W. B. & Sheng, R. The correlation between mitochondria-associated endoplasmic reticulum membranes (MAMs) and Ca(2+) transport in the pathogenesis of diseases. *Acta Pharm. Sin.* **46**, 271–291 (2025).
26. Kelley, N., Jeltema, D., Duan, Y. & He, Y. The NLRP3 inflammasome: an overview of mechanisms of activation and regulation. *Int. J. Mol. Sci*. **20**, 3328 (2019).
27. Tai, G. J. et al. NLRP3 inflammasome-mediated premature immunosenescence drives diabetic vascular aging dependent on the induction of perivascular adipose tissue dysfunction. *Cardiovasc Res* **121**, 77–96 (2025).
28. Wu, M. et al. Inhibition of NLRP3 inflammasome ameliorates podocyte damage by suppressing lipid accumulation in diabetic nephropathy. *Metabolism* **118**, 154748 (2021).
29. Lv, D. et al. Targeting phenylpyruvate restrains excessive NLRP3 inflammasome activation and pathological inflammation in diabetic wound healing. *Cell Rep. Med* **4**, 101129 (2023).
30. Li, C. et al. Macrophage M1 regulatory diabetic nephropathy is mediated by m6A methylation modification of lncRNA expression. *Mol. Immunol.* **144**, 16–25 (2022).
31. Schiffrin, E. L. & Pollock, D. M. Endothelin system in hypertension and chronic kidney disease. *Hypertension* **81**, 691–701 (2024).
32. Davenport, A. P. et al. Endothelin. *Pharm. Rev.* **68**, 357–418 (2016).
33. van Raalte, D. H. et al. Combination therapy for kidney disease in people with diabetes mellitus. *Nat. Rev. Nephrol.* **20**, 433–446 (2024).
34. Bonner, R., Albajrami, O., Hudspeth, J. & Upadhyay, A. Diabetic kidney disease. *Prim. Care* **47**, 645–659 (2020).
35. Cortinovis, M., Perico, N., Ruggenenti, P., Remuzzi, A. & Remuzzi, G. Glomerular hyperfiltration. *Nat. Rev. Nephrol.* **18**, 435–451 (2022).
36. Vallon, V. & Thomson, S. C. The tubular hypothesis of nephron filtration and diabetic kidney disease. *Nat. Rev. Nephrol.* **16**, 317–336 (2020).
37. Stefansson, V. T. N. et al. Molecular programs associated with glomerular hyperfiltration in early diabetic kidney disease. *Kidney Int.* **102**, 1345–1358 (2022).
38. Yao, X. et al. Klotho Ameliorates Podocyte Injury through Targeting TRPC6 Channel in Diabetic Nephropathy. *J. Diabetes Res.* **2022**, 1329380 (2022).
39. Qi, C. et al. Increased dishevelled associated activator of morphogenesis 2, a new podocyte-associated protein, in diabetic nephropathy. *Nephrol. Dial. Transpl.* **36**, 1006–1016 (2021).
40. Akhtar, M., Taha, N. M., Nauman, A., Mujeeb, I. B. & Al-Nabet, A. Diabetic kidney disease: past and present. *Adv. Anat. Pathol.* **27**, 87–97 (2020).
41. Susztak, K., Raff, A. C., Schiffer, M. & Bottinger, E. P. Glucose-induced reactive oxygen species cause apoptosis of podocytes and podocyte depletion at the onset of diabetic nephropathy. *Diabetes* **55**, 225–233 (2006).
42. Ducasa, G. M. et al. ATP-binding cassette A1 deficiency causes cardiolipin-driven mitochondrial dysfunction in podocytes. *J. Clin. Invest* **129**, 3387–3400 (2019).
43. Zhang, J. et al. ABCA1 deficiency-mediated glomerular cholesterol accumulation exacerbates glomerular endothelial injury and dysfunction in diabetic kidney disease. *Metabolism* **139**, 155377 (2023).
44. Mohandes, S. et al. Molecular pathways that drive diabetic kidney disease. *J. Clin. Investig*. **133**, e165654 (2023).
45. Wei, Y. et al. To target cellular senescence in diabetic kidney disease: the known and the unknown. *Clin. Sci.***138**, 991–1007 (2024).
46. Liang, D. et al. Metformin improves the senescence of renal tubular epithelial cells in a high-glucose state through E2F1. *Front Pharm.* **13**, 926211 (2022).
47. Eleftheriadis, T. et al. Dapagliflozin prevents high-glucose-induced cellular senescence in renal tubular epithelial cells. *Int. J. Mol. Sci*. **23**, 16107 (2022).
48. Nian, S. et al. The inhibitory effects of Dulaglutide on cellular senescence against high glucose in human retinal endothelial cells. *Hum. Cell* **35**, 995–1004 (2022).
49. Sugita, E., Hayashi, K., Hishikawa, A. & Itoh, H. Epigenetic alterations in podocytes in diabetic nephropathy. *Front Pharm.* **12**, 759299 (2021).
50. Fu, J., Lee, K., Chuang, P. Y., Liu, Z. & He, J. C. Glomerular endothelial cell injury and cross talk in diabetic kidney disease. *Am. J. Physiol. Ren. Physiol.* **308**, F287–F297 (2015).
51. Tanabe, K., Wada, J. & Sato, Y. Targeting angiogenesis and lymphangiogenesis in kidney disease. *Nat. Rev. Nephrol.* **16**, 289–303 (2020).
52. Schwager, S. & Detmar, M. Inflammation and Lymphatic Function. *Front Immunol.* **10**, 308 (2019).
53. Sandholm, N. et al. Genome-wide meta-analysis and omics integration identifies novel genes associated with diabetic kidney disease. *Diabetologia* **65**, 1495–1509 (2022).
54. Yao, L. et al. Mitochondrial dysfunction in diabetic tubulopathy. *Metabolism* **131**, 155195 (2022).
55. Kanbay, M. et al. Proximal tubule hypertrophy and hyperfunction: a novel pathophysiological feature in disease states. *Clin. Kidney J.* **17**, sfae195 (2024).

56. Juszczak, F., Caron, N., Mathew, A. V. & Decleves, A. E. Critical role for AMPK in metabolic disease-induced chronic kidney disease. *Int. J. Mol. Sci.* **21**, 7994 (2020).
57. Hong, Q. et al. Modulation of transforming growth factor-beta-induced kidney fibrosis by leucine-rich α-2 glycoprotein-1. *Kidney Int* **101**, 299–314 (2022).
58. Tang, S. C. W. & Yiu, W. H. Innate immunity in diabetic kidney disease. *Nat. Rev. Nephrol.* **16**, 206–222 (2020).
59. Yang, M. & Zhang, C. The role of innate immunity in diabetic nephropathy and their therapeutic consequences. *J. Pharm. Anal.* **14**, 39–51 (2024).
60. Braga, T. T. et al. MyD88 signaling pathway is involved in renal fibrosis by favoring a TH2 immune response and activating alternative M2 macrophages. *Mol. Med* **18**, 1231–1239 (2012).
61. Sierra-Mondragon, E. et al. All-trans retinoic acid ameliorates inflammatory response mediated by TLR4/NF-kappaB during initiation of diabetic nephropathy. *J. Nutr. Biochem* **60**, 47–60 (2018).
62. Zhao, W. et al. Metabolic Dysfunction in the Regulation of the NLRP3 Inflammasome Activation: A Potential Target for Diabetic Nephropathy. *J. Diabetes Res* **2022**, 2193768 (2022).
63. Lu, Q. et al. Complement factor B in high glucose-induced podocyte injury and diabetic kidney disease. *JCI Insight*. **6**, e147716 (2021).
64. Duan, S. et al. Association of glomerular complement C4c deposition with the progression of diabetic kidney disease in patients with type 2 diabetes. *Front. Immunol.* **11**, 2073 (2020).
65. Sircar, M. et al. Complement 7 is up-regulated in human early diabetic kidney disease. *Am. J. Pathol.* **188**, 2147–2154 (2018).
66. Trambas, I. A., Coughlan, M. T. & Tan, S. M. Therapeutic potential of targeting complement C5a receptors in diabetic kidney disease. *Int. J. Mol. Sci.* **24**, 8758 (2023).
67. Satoskar, A. A. et al. Characterization of glomerular diseases using proteomic analysis of laser capture microdissected glomeruli. *Mod. Pathol.* **25**, 709–721 (2012).
68. Li, L. et al. C3a and C5a receptor antagonists ameliorate endothelial-myofibroblast transition via the Wnt/beta-catenin signaling pathway in diabetic kidney disease. *Metabolism* **64**, 597–610 (2015).
69. Xu, Z., Tao, L. & Su, H. The complement system in metabolic-associated kidney
70. Flyvbjerg, A. The role of the complement system in diabetic nephropathy. *Nat. Rev. Nephrol.* **13**, 311–318 (2017).
71. Rayego-Mateos, S. et al. Targeting inflammation to treat diabetic kidney disease: the road to 2030. *Kidney Int.* **103**, 282–296 (2023).
72. Yang, T. et al. An update on chronic complications of diabetes mellitus: from molecular mechanisms to therapeutic strategies with a focus on metabolic memory. *Mol. Med.* **30**, 71 (2024).
73. Kato, M. & Natarajan, R. Epigenetics and epigenomics in diabetic kidney disease and metabolic memory. *Nat. Rev. Nephrol.* **15**, 327–345 (2019).
74. Yoshimoto, N. et al. Significance of podocyte DNA damage and glomerular DNA methylation in CKD patients with proteinuria. *Hypertens. Res.* **46**, 1000–1008 (2023).
75. Gu, X. et al. N6-methyladenosine demethylase FTO promotes M1 and M2 macrophage activation. *Cell Signal* **69**, 109553 (2020).
76. Ma, C. X. et al. Cardiovascular disease in type 2 diabetes mellitus: progress toward personalized management. *Cardiovasc. Diabetol.* **21**, 74 (2022).
77. Kozakova, M., Morizzo, C., Fraser, A. G. & Palombo, C. Impact of glycemic control on aortic stiffness, left ventricular mass and diastolic longitudinal function in type 2 diabetes mellitus. *Cardiovasc. Diabetol.* **16**, 78 (2017).
78. Medina-Leyte, D. J. et al. Endothelial dysfunction, inflammation and coronary artery disease: potential biomarkers and promising therapeutical approaches. *Int. J. Mol. Sci.* **22**, 3850 (2021).
79. Saenz-Medina, J. et al. Endothelial dysfunction: an intermediate clinical feature between urolithiasis and cardiovascular diseases. *Int. J. Mol. Sci.* **23**, 912 (2022).
80. Montanaro, R. et al. Hydrogen sulfide donor AP123 restores endothelial nitric oxide-dependent vascular function in hyperglycemia via a CREB-dependent pathway. *Redox Biol.* **62**, 102657 (2023).
81. Zhang, X. et al. Ion channel Piezo1 activation aggravates the endothelial dysfunction under a high glucose environment. *Cardiovasc. Diabetol.* **23**, 150 (2024).
82. Yao, Y. et al. Endothelial cell metabolic memory causes cardiovascular dysfunction in diabetes. *Cardiovasc. Res.* **118**, 196–211 (2022).
83. Huang, Q. et al. Uncovering endothelial to mesenchymal transition drivers in atherosclerosis via multi-omics analysis. *BMC Cardiovasc. Disord.* **25**, 104 (2025).
84. Zhao, G. et al. Endothelial KLF11 is a novel protector against diabetic atherosclerosis. *Cardiovasc. Diabetol.* **23**, 381 (2024).
85. Liu, L. et al. Bone marrow mesenchymal stem cell-derived extracellular vesicles alleviate diabetes-exacerbated atherosclerosis via AMPK/mTOR pathway-mediated autophagy-related macrophage polarization. *Cardiovasc. Diabetol.* **24**, 48 (2025).
86. Bai, X. et al. CAV1-CAVIN1-LC3B-mediated autophagy regulates high glucose-stimulated LDL transcytosis. *Autophagy* **16**, 1111–1129 (2020).
87. Zhang, Z. et al. USF1 transcriptionally activates USP14 to drive atherosclerosis by promoting EndMT through NLRC5/Smad2/3 axis. *Mol. Med.* **30**, 32 (2024).

88. Cheng, C. K. et al. SOX4 is a novel phenotypic regulator of endothelial cells in atherosclerosis revealed by single-cell analysis. *J. Adv. Res* **43**, 187–203 (2023).
89. Supinski, G. S., Schroder, E. A. & Callahan, L. A. Mitochondria and critical illness. *Chest* **157**, 310–322 (2020).
90. Zhang, Y. et al. Liraglutide prevents high glucose induced HUVECs dysfunction via inhibition of PINK1/Parkin-dependent mitophagy. *Mol. Cell Endocrinol.* **545**, 111560 (2022).
91. Heather, L. C., Gopal, K., Srnic, N. & Ussher, J. R. Redefining diabetic cardiomyopathy: perturbations in substrate metabolism at the heart of its pathology. *Diabetes* **73**, 659–670 (2024).
92. Zhang, Y., Zhang, Z., Tu, C., Chen, X. & He, R. Advanced glycation end products in disease development and potential interventions. *Antioxidants***14**, 492 (2025).
93. Bansal, S., Burman, A. & Tripathi, A. K. Advanced glycation end products: key mediator and therapeutic target of cardiovascular complications in diabetes. *World J. Diabetes* **14**, 1146–1162 (2023).
94. Souders, C. A., Bowers, S. L. & Baudino, T. A. Cardiac fibroblast: the renaissance cell. *Circ. Res* **105**, 1164–1176 (2009).
95. Ndumele, C. E. et al. A synopsis of the evidence for the science and clinical management of cardiovascular-kidney-metabolic (CKM) syndrome: a scientific statement from the American Heart Association. *Circulation* **148**, 1636–1664 (2023).
96. Meng, L. et al. METTL14 suppresses pyroptosis and diabetic cardiomyopathy by downregulating TINCR lncRNA. *Cell Death Dis.* **13**, 38 (2022).
97. Maisch, B., Alter, P. & Pankuweit, S. Diabetic cardiomyopathy–fact or fiction?. *Herz* **36**, 102–115 (2011).
98. Falcao-Pires, I. & Leite-Moreira, A. F. Diabetic cardiomyopathy: understanding the molecular and cellular basis to progress in diagnosis and treatment. *Heart Fail. Rev.* **17**, 325–344 (2012).
99. Sun, Q., Karwi, Q. G., Wong, N. & Lopaschuk, G. D. Advances in myocardial energy metabolism: metabolic remodelling in heart failure and beyond. *Cardiovasc. Res.* **120**, 1996–2016 (2024).
100. McDonagh, T. A. et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur. Heart J.* **42**, 3599–3726 (2021).
101. Gladden, J. D., Chaanine, A. H. & Redfield, M. M. Heart failure with preserved ejection fraction. *Annu. Rev. Med.* **69**, 65–79 (2018).
102. Dia, M. et al. Effect of metformin on T2D-induced MAM Ca(2+) uncoupling and contractile dysfunction in an early mouse model of diabetic HFpEF. *Int. J. Mol. Sci.* **23**, 3569 (2022).
103. Lazo, M. et al. Soluble receptor for advanced glycation end products and the risk for incident heart failure: the atherosclerosis risk in communities study. *Am. Heart J.* **170**, 961–967 (2015).
104. Ren, J., Wu, N. N., Wang, S., Sowers, J. R. & Zhang, Y. Obesity cardiomyopathy: evidence, mechanisms, and therapeutic implications. *Physiol. Rev.* **101**, 1745–1807 (2021).
105. Nagayach, A. et al. Advancing the understanding of diabetic encephalopathy through unravelling pathogenesis and exploring future treatment perspectives. *Ageing Res. Rev.* **100**, 102450 (2024).
106. Nie, S. D. et al. High glucose forces a positive feedback loop connecting ErbB4 expression and mTOR/S6K pathway to aggravate the formation of tau hyperphosphorylation in differentiated SH-SY5Y cells. *Neurobiol. Aging* **67**, 171–180 (2018).
107. Yang, Y. et al. The imbalance of PGD2-DPs pathway is involved in the type 2 diabetes brain injury by regulating autophagy. *Int. J. Biol. Sci.* **17**, 3993–4004 (2021).
108. Taile, J., Arcambal, A., Clerc, P., Gauvin-Bialecki, A. & Gonthier, M. P. Medicinal plant polyphenols attenuate oxidative stress and improve inflammatory and vasoactive markers in cerebral endothelial cells during hyperglycemic condition. *Antioxidants***9**, 573 (2020).
109. Lee, K. S. et al. Hyperglycemia enhances brain susceptibility to lipopolysaccharide-induced neuroinflammation via astrocyte reprogramming. *J. Neuroinflamm.* **21**, 137 (2024).
110. Ge, X. et al. Electroacupuncture improves cognitive impairment in diabetic cognitive dysfunction rats by regulating the mitochondrial autophagy pathway. *J. Physiol. Sci.* **72**, 29 (2022).
111. Zhao, H. et al. Hydrogen sulfide plays an important role by regulating endoplasmic reticulum stress in diabetes-related diseases. *Int. J. Mol. Sci.* **23**, 7170 (2022).
112. Sousa, L., Oliveira, M. M., Pessoa, M. T. C. & Barbosa, L. A. Iron overload: effects on cellular biochemistry. *Clin. Chim. Acta* **504**, 180–189 (2020).
113. Swain, S. K., Chandra Dash, U. & Sahoo, A. K. Hydrolea zeylanica improves cognitive impairment in high-fat diet fed-streptozotocin-induced diabetic encephalopathy in rats via regulating oxidative stress, neuroinflammation, and neurotransmission in brain. *Heliyon* **8**, e11301 (2022).
114. Golledge, J. Update on the pathophysiology and medical treatment of peripheral artery disease. *Nat. Rev. Cardiol.* **19**, 456–474 (2022).
115. Jude, E. B., Oyibo, S. O., Chalmers, N. & Boulton, A. J. Peripheral arterial disease in diabetic and nondiabetic patients: a comparison of severity and outcome. *Diabetes Care* **24**, 1433–1437 (2001).
116. Mozes, G. et al. Atherosclerosis in amputated legs of patients with and without diabetes mellitus. *Int. Angiol.* **17**, 282–286 (1998).
117. Nikolajevic, J. & Sabovic, M. Inflammatory, metabolic, and coagulation effects on medial arterial calcification in patients with peripheral arterial disease. *Int. J. Mol. Sci*. **24**, 3132 (2023).

118. Zayed, M. G. et al. Diabetic retinopathy and quality of life: a systematic review and meta-analysis. *JAMA Ophthalmol.* **142**, 199–207 (2024).
119. Ling, F., Zhang, C., Zhao, X., Xin, X. & Zhao, S. Identification of key genes modules linking diabetic retinopathy and circadian rhythm. *Front. Immunol.* **14**, 1260350 (2023).
120. Wong, T. Y., Cheung, C. M., Larsen, M., Sharma, S. & Simo, R. Diabetic retinopathy. *Nat. Rev. Dis. Prim.* **2**, 16012 (2016).
121. Hassan, J. W. & Bhatwadekar, A. D. Senolytics in the treatment of diabetic retinopathy. *Front. Pharm.* **13**, 896907 (2022).
122. Han, X. Y. et al. Targeting endothelial glycolytic reprogramming by tsRNA-1599 for ocular anti-angiogenesis therapy. *Theranostics* **14**, 3509–3525 (2024).
123. Yu, F. et al. Dynamic O-GlcNAcylation coordinates ferritinophagy and mitophagy to activate ferroptosis. *Cell Discov.* **8**, 40 (2022).
124. Zhang, J., Qiu, Q., Wang, H., Chen, C. & Luo, D. TRIM46 contributes to high glucose-induced ferroptosis and cell growth inhibition in human retinal capillary endothelial cells by facilitating GPX4 ubiquitination. *Exp. Cell Res.* **407**, 112800 (2021).
125. Gu, C. et al. miR-590-3p inhibits pyroptosis in diabetic retinopathy by targeting NLRP1 and inactivating the NOX4 signaling pathway. *Investig. Ophthalmol. Vis. Sci.* **60**, 4215–4223 (2019).
126. Wang, Q. et al. Poly (ADP-ribose) polymerase 1 mediated arginase II activation is responsible for oxidized LDL-induced endothelial dysfunction. *Front Pharm.* **9**, 882 (2018).
127. Oshitari, T. Neurovascular cell death and therapeutic strategies for diabetic retinopathy. *Int. J. Mol. Sci*. **24**, 12919 (2023).
128. Li, L. et al. Ferroptosis: new insight into the mechanisms of diabetic nephropathy and retinopathy. *Front Endocrinol. (Lausanne)* **14**, 1215292 (2023).
129. Wolf, J. et al. Liquid-biopsy proteomics combined with AI identifies cellular drivers of eye aging and disease in vivo. *Cell* **186**, 4868–4884.e4812 (2023).
130. Yao, Y. et al. Macrophage/microglia polarization for the treatment of diabetic retinopathy. *Front Endocrinology***14**, 1276225 (2023).
131. Lv, K. et al. Integrated multi-omics reveals the activated retinal microglia with intracellular metabolic reprogramming contributes to inflammation in STZ-induced early diabetic retinopathy. *Front. Immunol.* **13**, 942768 (2022).
132. Ben, S. et al. Microglia-endothelial cross-talk regulates diabetes-induced retinal vascular dysfunction through remodeling inflammatory microenvironment. *iScience* **27**, 109145 (2024).
133. Xu, Y. et al. Single-cell transcriptomes reveal a molecular link between diabetic kidney and retinal lesions. *Commun. Biol.* **6**, 912 (2023).
134. He, C. et al. A specific RIP3(+) subpopulation of microglia promotes retinopathy through a hypoxia-triggered necroptotic mechanism. *Proc. Natl Acad. Sci. USA* **118**, e2023290118 (2021).
135. Binet, F. et al. Neutrophil extracellular traps target senescent vasculature for tissue remodeling in retinopathy. *Science* **369**, eaay5356 (2020).
136. Zhang, X., Zhang, F. & Xu, X. Single-cell RNA sequencing in exploring the pathogenesis of diabetic retinopathy. *Clin. Transl. Med.* **14**, e1751 (2024).
137. Van Hove, I. et al. Single-cell transcriptome analysis of the Akimba mouse retina reveals cell-type-specific insights into the pathobiology of diabetic retinopathy. *Diabetologia* **63**, 2235–2248 (2020).
138. Zhang, X. et al. Association of plasma osteopontin with diabetic retinopathy in Asians with type 2 diabetes. *Mol. Vis.* **24**, 165–173 (2018).
139. Bai, C. W. et al. G protein subunit alpha i2 pivotal role in angiogenesis. *Theranostics* **14**, 2190–2209 (2024).