

Review

Advances in Diabetes-Induced Microvascular Pathology and Therapeutic Strategies: A Mini-Review

Jifeng Xiao^{1,†}, Wenping Wu^{1,†}, Junqi Peng^{2,3,4}, Hanqing Zhang^{2,3,4}, Yun Wu^{2,3,4},
Song Chen^{2,3,4,*}

¹The Second Clinical College of Wuhan University, 430071 Wuhan, Hubei, China

²Department of Cardiovascular Surgery, Zhongnan Hospital of Wuhan University, 430071 Wuhan, Hubei, China

³Hubei Provincial Engineering Research Center of Minimally Invasive Cardiovascular Surgery, 430071 Wuhan, Hubei, China

⁴Wuhan Clinical Research Center for Minimally Invasive Treatment of Structural Heart Disease, 430071 Wuhan, Hubei, China

*Correspondence: song.chen@whu.edu.cn (Song Chen)

†These authors contributed equally.

Academic Editors: Gabriella Lupo and Paramjit S. Tappia

Submitted: 4 September 2025 Revised: 30 March 2026 Accepted: 17 April 2026 Published: 28 October 2026

Abstract

Diabetes mellitus (DM) is a metabolic disorder characterized by hyperglycemia that drives chronic complications through microvascular damage. This mini-review systematically examines the molecular mechanisms, clinical manifestations, and therapeutic prospects of diabetes-associated microvascular pathologies. Sustained hyperglycemia triggers microvascular dysfunction via activation of the polyol pathway, accumulation of advanced glycation end products (AGEs), excessive generation of reactive oxygen species (ROS), and dysregulated protein kinase C (PKC) signaling. These processes collectively induce endothelial impairment, oxidative stress, and chronic inflammation. The major clinical complications are diabetic nephropathy, retinopathy, and neuropathy, which contribute significantly to morbidity and mortality. Conventional therapies focus on glycemic control with insulin, metformin, and newer agents such as sodium-glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists. However, targeted strategies addressing microvascular damage remain limited. Emerging approaches, including antioxidants gene-editing technologies (CRISPR/Cas9), and stem cell-based interventions (mesenchymal stem cells), show potential for vascular repair. Their safety and long-term efficacy require further validation. Future research should integrate multi-omics methodologies to address individual heterogeneity, advance precision medicine, and optimize synergistic therapeutic combinations to reduce the global burden of diabetic microvascular complications.

Keywords: diabetes mellitus; microvascular complications; oxidative stress; advanced glycation end products; therapeutic strategies

1. Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder and a major global public health challenge due to its rising prevalence [1]. Recent estimates suggest that over 828 million adults are affected worldwide, including approximately 148 million in China [2]. The disease is characterized by persistent hyperglycemia resulting from impaired insulin secretion, insulin action, or both, leading to dysregulation of carbohydrate, lipid, and protein metabolism. Beyond its direct effects on quality of life, DM is strongly associated with microvascular complications, including diabetic retinopathy, nephropathy, and neuropathy [3]. These complications are the primary drivers of disability and mortality in DM patients and represent a significant clinical and economic burden.

Despite advances in diabetes management, effective targeted therapies for microvascular damage remain limited. This underscores the urgent need to elucidate the underlying pathophysiological mechanisms to develop better preventive and therapeutic strategies. Oxidative stress is widely recognized as a central unifying mechanism link-

ing hyperglycemia to endothelial dysfunction, inflammation, and tissue damage in the microvasculature [4].

This mini-review provides an updated overview of diabetes-induced microvascular pathology. It begins with fundamental concepts of diabetes and the microvascular system, followed by a detailed examination of the key molecular mechanisms—particularly oxidative stress and its interconnected pathways. Clinical manifestations of major microvascular complications are described, and current therapeutic strategies, including conventional pharmacotherapy, adjunctive measures, gene therapy, and stem cell approaches, are evaluated. Finally, future perspectives on precision medicine and novel interventions are discussed. By integrating mechanistic insights with therapeutic prospects, this review aims to highlight promising directions for alleviating the global impact of diabetic microvascular complications.

2. Diabetes

DM is a metabolic disorder characterized by defects in insulin secretion or action, leading to the dysregulated metabolism of carbohydrates, lipids, and proteins. Its clinical



cal manifestation is marked by chronic hyperglycemia. The disease encompasses several subtypes, including type 1 diabetes (T1DM), type 2 diabetes (T2DM), gestational diabetes (GDM), and neonatal diabetes (NDM), with T1DM and T2DM representing the predominant clinical forms [2,5,6]. T1DM is a chronic autoimmune disorder resulting from immune-mediated destruction of pancreatic β -cells, causing absolute insulin deficiency and consequent hyperglycemia [7,8]. This process involves infiltration of the pancreatic islets by CD4⁺ and CD8⁺ T lymphocytes and macrophages, initiating autoimmune injury to the β -cells [9,10]. In contrast, the pathogenesis of T2DM primarily stems from non-autoimmune β -cell failure. Key mechanisms include β -cell dedifferentiation, oxidative stress, chronic low-grade inflammation, and mitochondrial dysfunction. These pathological changes impair the adaptive capacity of β -cells to chronic nutrient excess, thereby promoting glucotoxicity, insulin resistance, and obesity [11,12]. Genetic predisposition plays a significant role in both types. Approximately 568 genetic loci are associated with T2DM and 136 with T1DM. Environmental factors, such as viral infections, gut dysbiosis, diet, and lifestyle, also contribute to disease development [13].

Oxidative stress and inflammation serve as shared mechanisms in both T1DM and T2DM. They link hyperglycemia to vascular injury and set the stage for microvascular complications.

3. Microvascular System

The microcirculation consists of small vessels (typically <100 μ m in diameter) with a high surface-area-to-volume ratio. It facilitates rapid exchange of oxygen, nutrients, hormones, and waste products between blood and tissues [14]. Microvessels are critical for meeting the metabolic demands of parenchymal cells and maintaining organ function.

Microcirculatory beds in the retina, brain, and peripheral nerves share similar structures. They feature continuous endothelial cells connected by tight junctions, along with pericytes and a basement membrane. These components form the blood-retinal barrier, blood-brain barrier, and blood-nerve barrier, respectively. These barriers protect neural tissues while supplying high levels of glucose and oxygen. The microvasculature is highly vulnerable to sustained hyperglycemia, which can lead to structural and functional damage. Such injury, combined with impaired repair mechanisms, underlies diabetic microvascular complications in both T1DM and T2DM [15,16].

4. Mechanisms of Microvascular Damage Induced by Diabetes

The pathological manifestations of diabetes and its microvascular complications encompass multiple processes, including hyperglycemia, dyslipidemia, dysfunction, coagulopathy, and chronic inflammatory burden. How-

ever, both clinical and basic research consistently identify chronic hyperglycemia as the common initiating factor underlying these abnormalities [17]. Chronic hyperglycemia initiates microvascular injury through multiple interconnected pathways. These pathways converge on oxidative stress as a central driver. Therefore, oxidative stress can be regarded as a unifying mechanism that links hyperglycemia to various forms of vascular injury, and whose downstream effects ultimately drive the onset and progression of diabetic microvascular complications [18]. Table 1 (Ref. [19,20,21,22]) summarizes the microvascular alterations induced by diabetes.

4.1 Oxidative Stress and Inflammation

Oxidative stress occurs when reactive oxygen species (ROS) production exceeds antioxidant defenses, causing damage to biomolecules. In diabetes, hyperglycemia drives mitochondrial superoxide overproduction. This activates downstream pathways, including poly (ADP-ribose) polymerase (PARP) overactivation, which depletes NAD⁺ and inhibits glyceraldehyde-3-phosphate dehydrogenase (GAPDH). The resulting accumulation of glycolytic intermediates amplifies ROS and triggers inflammation via nuclear factor kappa-B (NF- κ B) and NLRP3 inflammasome activation [23].

Nuclear factor erythroid 2-related factor 2 (Nrf2) is a key regulator of antioxidant responses. Under oxidative stress, Nrf2 translocates to the nucleus and upregulates genes such as heme oxygenase-1 (HO-1), NAD(P)H quinone oxidoreductase 1 (NQO1), superoxide dismutase (SOD), and catalase (CAT). Activation of Nrf2 has shown protective effects in experimental models of diabetic complications [24].

Mitochondrial biogenesis factors, including peroxisome proliferator-activated receptor gamma coactivator 1- α (PGC-1 α), Nrf1/2, and mitochondrial transcription factor A (TFAM), help restore energy homeostasis. However, persistent ROS can overwhelm these defenses, perpetuating a vicious cycle of endothelial dysfunction and inflammation [25].

4.2 Generation of Advanced Glycation End Products (AGEs)

AGEs form through non-enzymatic glycation of proteins, lipids, and nucleic acids under hyperglycemia. AGEs bind to the receptor for AGEs (receptor for advanced glycation end products [RAGE]), activating MAPK, NF- κ B, and protein kinase C (PKC) pathways. This increases ROS and inflammation while altering extracellular matrix structure and promoting insulin resistance [26,27].

4.3 Excessive Activation of PKC Isoforms

Hyperglycemia elevates diacylglycerol (DAG), which activates PKC isoforms (particularly PKC- β). Activated PKC enhances nicotinamide adenine dinucleotide phos-

Table 1. Diabetes-induced microvascular changes.

Target organs	Microvascular changes
Retina	Thickening of the capillary basement membrane; pericyte loss; microaneurysm formation; neovascularization [19,20]
Kidney	Glomerular hypertrophy, glomerular basement membrane thickening and injury [21]
Brain (Microvascular)	Increased blood-brain barrier permeability; lacunar infarcts; microbleeds; white matter hyperintensities (WMHs) [22]
Peripheral nerves	Thickening of the endoneurial capillary basement membrane with luminal narrowing; vascular endothelial dysfunction [20]

phate (NADPH) oxidase activity, Vascular Endothelial Growth Factor (VEGF) expression, and NF- κ B signaling, leading to increased permeability, angiogenesis, and vascular dysfunction [28,29].

4.4 Hexosamine Biosynthetic Pathway

Excess glucose is shunted into the hexosamine pathway via glutamine:fructose-6-phosphate amidotransferase (GFAT). This produces uridine diphosphate N-acetylglucosamine (UDP-GlcNAc), which modifies proteins via O-GlcNAcylation. The pathway exacerbates insulin resistance, oxidative stress, and inflammatory signaling [30,31].

4.5 Polyol Pathway

Aldose reductase converts glucose to sorbitol, consuming NADPH and generating fructose. Sorbitol accumulation causes osmotic stress, while NADPH depletion impairs glutathione regeneration, further increasing oxidative stress. This pathway also feeds into AGE and PKC activation [32].

Hyperglycemia links the four classical pathways (formation of AGEs, PKC activation, the hexosamine biosynthetic pathway [HBP], and the polyol pathway) through a common upstream event: “mitochondrial superoxide overproduction”. This forms a self-amplifying network that ultimately leads to diabetic microvascular complications.

Initially, the hyperglycemic environment increases electron flux through the mitochondrial electron transport chain, triggering a burst of superoxide (O_2^-) and elevated ROS production. Excess ROS inhibits the key glycolytic enzyme GAPDH, causing upstream glycolytic intermediates to accumulate.

The four classical pathways (AGEs-PKC-HBP-polyol) provide positive feedback, continuously generating secondary ROS. Accumulated glyceraldehyde-3-phosphate undergoes spontaneous oxidation to form methylglyoxal (MGO), a potent precursor for AGEs. The binding of AGEs to RAGE activates NADPH oxidase, leading to sustained ROS production. This combined ROS (mitochondrial and NADPH oxidase-derived) further inhibits GAPDH, perpetuating the cycle.

Glycolytic intermediates are converted into DAG, which directly activates PKC β . This, in turn, activates

NADPH oxidase, generating additional ROS. Meanwhile, F6P is diverted into the HBP to produce UDP-GlcNAc, which modifies PKC and transcription factors via O-GlcNAcylation, thereby amplifying inflammatory and fibrotic signaling.

Excess glucose is reduced to sorbitol in the polyol pathway, consuming NADPH and depleting reduced glutathione, which subsequently exacerbates oxidative stress and generates additional MGO. The glycolytic intermediate F6P accumulates and is catalyzed by the rate-limiting enzyme GFAT to enter the HBP, leading to a sharp increase in the end product UDP-GlcNAc. This subsequently mediates O-linked N-acetylglucosamine (O-GlcNAc) modifications to various proteins, which can activate PKC and NADPH oxidase (NOX) subunits, further generating ROS and inhibiting GAPDH.

As ROS levels continue to rise, the body activates the Nrf2 signaling pathway and mitochondrial biogenesis factors to counteract oxidative stress. However, PARP overactivation antagonistically consumes NAD^+ , leading to aberrant metabolic and functional changes in the mitochondria and increasing ROS production. Through these complex interactions among pathways, hyperglycemia ultimately leads to endothelial dysfunction, thickening of the basement membrane (BM), and chronic inflammation, all of which are key processes in the onset and progression of diabetic microvascular complications.

Therefore, mitochondrial ROS acts as the “master switch”, while Nrf2, PARP, and mitochondrial biogenesis factors interact to modulate ROS levels. The four classical pathways function as interlocking amplifiers, collectively driving the triad of molecular events (endothelial injury, ECM accumulation, and chronic inflammation) that constitute the core mechanism of diabetic microvascular complications (Fig. 1).

5. Clinical Manifestations of Diabetic Microvascular Damage

5.1 Diabetic Kidney Disease (DKD)

Diabetic microvascular diseases are major causes of morbidity and mortality among individuals with diabetes [33]. Among the various complications, diabetic kidney disease (DKD) is a prevalent global health issue characterized by the progressive decline in renal function due

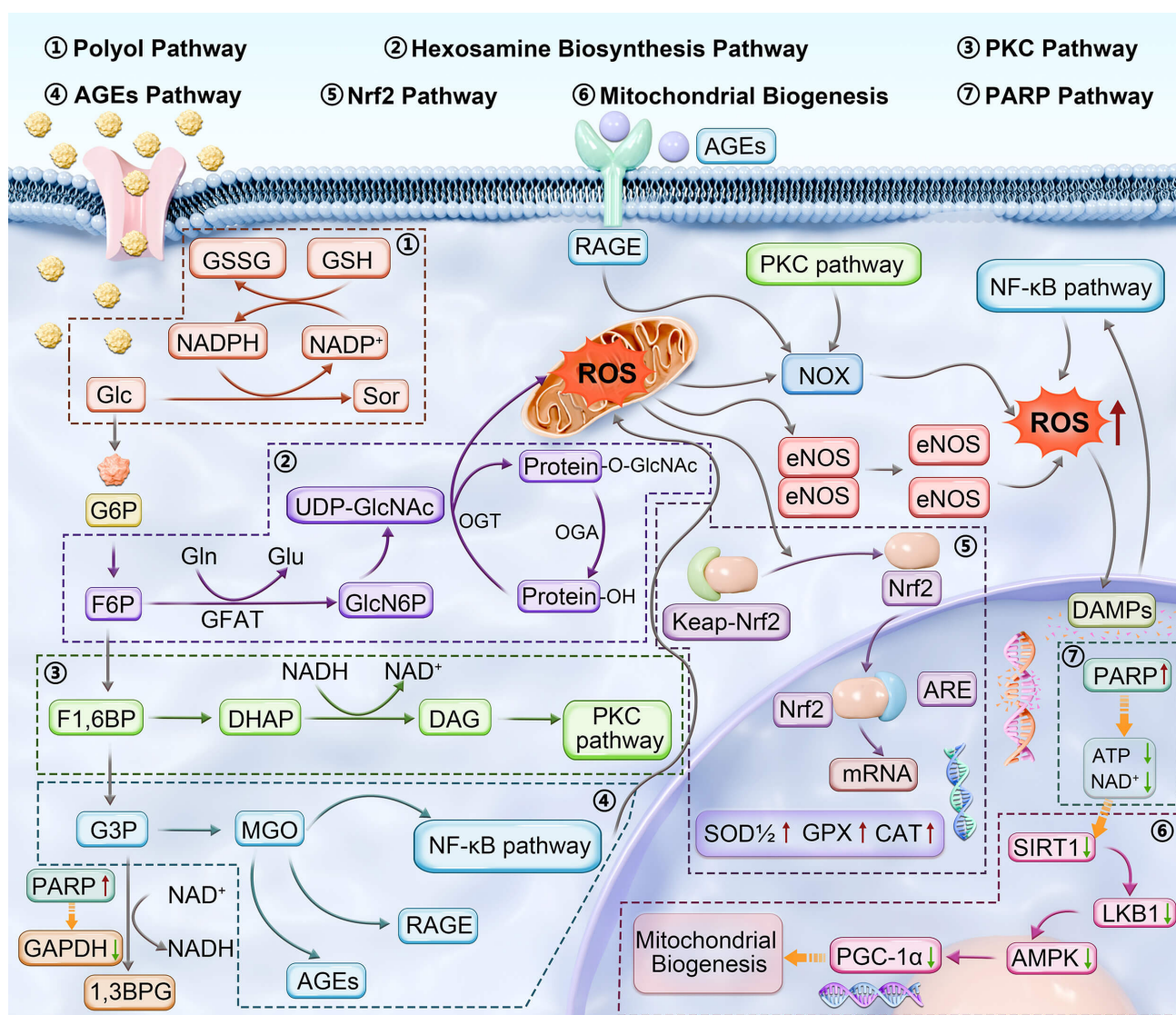


Fig. 1. Oxidative stress mechanisms in diabetes. PKC, protein kinase C; AGEs, advanced glycation end products; Nrf2, nuclear factor erythroid 2-related factor 2; PARP, poly (ADP-ribose) polymerase; GSSG, glutathione disulfide; GSH, intracellular glutathione; NADPH, nicotinamide adenine dinucleotide phosphate; GFAT, glutamine, fructose-6-phosphate amidotransferase; UDP-GlcNAc, uridine diphosphate N-acetylglucosamine; OGT, O-GlcNAc transferase; OGA, O-GlcNAcase; ROS, reactive oxygen species; NOX, NADPH oxidase; eNOS, endothelial nitric oxide synthase; NF-κB, nuclear factor kappa-B; DHAP, dihydroxyacetone phosphate; DAG, diacylglycerol; MGO, methylglyoxal; RAGE, receptor for Advanced Glycation End Products; ARE, antioxidant response element; mRNA, messenger RNA; SOD, superoxide dismutase; GPX, glutathione peroxidase; CAT, catalase; SIRT1, silent mating type information regulation 2 homolog-1; LKB1, liver kinase B1; AMPK, AMP-activated protein kinase; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; ATP, adenosine triphosphate; DAMPs, damage-associated molecular patterns. Blender (Blender 4.0) was used for images creating, and GIMP (GIMP 2.10) was used for image layout.

to hyperglycemia, often accompanied by proteinuria. Approximately 30% to 40% of diabetic patients progress to DKD, significantly increasing their morbidity and mortality [34]. Despite available treatment options, the risk of disease progression remains considerable, highlighting the urgent need for a deeper understanding of the underlying molecular mechanisms.

Disturbances in glucose metabolism caused by hyperglycemia can trigger a series of metabolic, hemodynamic,

inflammatory, and fibrotic processes that contribute to the onset and progression of DKD. Current research focuses on the roles of inflammation and fibrosis-related factors. Although these have not yet been widely recognized as therapeutic targets, an accumulating body of evidence supports their critical roles in the pathology of DKD [35]. Additionally, mitochondrial dysfunction is considered to be a key early event in the development of DKD, and growing evidence suggests that restoring mitochondrial function

may help to impede the progression of DKD. Strategies that aim to restore mitochondrial biogenesis and dynamics may therefore present new therapeutic opportunities. As we gain a deeper understanding of the importance of mitochondrial function, treatment approaches for DKD and other renal diseases that enhance mitochondrial function could hold significant value [36].

5.2 Diabetic Retinopathy (DR)

Diabetic retinopathy (DR) is a common and serious ocular complication among patients with diabetes. Its occurrence is closely related to the duration of diabetes, inadequate management of blood glucose and blood pressure, as well as an increased risk of other systemic vascular issues. In recent years, the widespread adoption of modern technologies such as optical coherence tomography (OCT) imaging and anti-VEGF therapies has significantly improved the diagnosis and treatment outcomes for DR. The global burden of DR is projected to increase by 2030, shifting from high-income countries to low- and middle-income regions. Concurrently, artificial intelligence is gradually being applied in the screening and diagnosis of DR. New drugs and therapeutic strategies, including gene therapy, are expected to be incorporated into the management of DR. Moreover, current treatment approaches are continuously evolving, including laser therapy, intravitreal injections of steroids or anti-VEGF agents, and vitrectomy. Future advances may include novel regenerative therapies and methods for targeting angiogenic factors [37,38].

5.3 Diabetic Peripheral Neuropathy (DPN)

Diabetic peripheral neuropathy (DPN) is a prevalent chronic complication of diabetes that significantly affects nerve function and muscle strength, resulting in difficulties with balance. Its occurrence is closely associated with diabetes duration, age, glycated hemoglobin (HbA1c), and DR, with these factors shown to significantly increase the risk of peripheral neuropathy in diabetic patients. This provides important insights into the etiology of DPN and its prevention strategies [39].

Research has evaluated the therapeutic effects of 10 kHz spinal cord stimulation (SCS) in refractory patients with painful DPN, which may represent a new treatment option for such cases [40]. In patients with T2DM, an 8-week combined resistance and aerobic training regimen positively affected serum neurotrophic factor-1 and physical function, with patients showing a significant increase in lower body strength. This suggests that exercise training could potentially be useful for the management of DPN, though further validation is needed [41]. Although the current clinical trials did not demonstrate significant efficacy, SCS and combined resistance-aerobic training may provide new therapeutic avenues for improving diabetic neuropathy.

Diabetic microvascular complications commonly include diabetic retinopathy, diabetic nephropathy, diabetic cerebral microvascular disease, and peripheral vascular disease. Diabetic retinopathy is asymptomatic in the early stages, with fundoscopic examination revealing microaneurysms, hemorrhages, and hard exudates; it progresses in advanced stages to macular edema, vitreous hemorrhage, and retinal detachment, potentially resulting in severe vision loss or blindness. Cerebral microvascular damage leads to cognitive decline and cerebral atrophy (diabetic encephalopathy), increasing the risk of dementia. Renal microvascular damage initially presents with microalbuminuria, progressively developing into overt proteinuria, edema, renal insufficiency, and potentially end-stage renal disease (ESRD). Peripheral vascular injury often coexists with peripheral neuropathy, characterized by symmetric limb numbness, tingling, and burning sensations; symptoms often worsen at night, presenting as diminished sensation or hyperalgesia (Fig. 2).

6. Oxidative Stress in Organ-Specific Microvascular Complications of Diabetes

6.1 Kidney (Diabetic Nephropathy Disease)

Diabetic nephropathy is one of the most common microvascular complications, characterized by progressive glomerular injury and renal dysfunction. Oxidative stress plays a pivotal role by promoting mesangial expansion, podocyte apoptosis, and the accumulation of ECM. Hyperglycemia-induced overproduction of ROS in mitochondria and the activation of NADPH oxidase lead to thickening of the glomerular BM and tubulointerstitial fibrosis [42,43]. Therapeutic strategies targeting oxidative stress, such as Nrf2 activators and antioxidants, have shown promise in experimental models [44].

6.2 Retina (Diabetic Retinopathy)

Diabetic retinopathy is a leading cause of blindness worldwide. Oxidative stress contributes to retinal microvascular damage through pericyte loss, endothelial dysfunction, and increased vascular permeability. ROS-mediated activation of inflammatory pathways (e.g., NF- κ B, VEGF signaling) exacerbates neovascularization and capillary drop-out [45]. Antioxidant therapies, including polyphenols and mitochondrial-targeted agents, have shown protective effects in preclinical studies [46].

6.3 Cardiovascular System: Diabetic Cardiomyopathy and Microvascular Dysfunction

Cardiovascular microvascular complications in diabetes manifest as impaired coronary microcirculation and diabetic cardiomyopathy. Oxidative stress induces endothelial dysfunction, reduces the bioavailability of nitric oxide, and promotes myocardial fibrosis. Mitochondrial ROS and AGEs synergistically impair cardiac microvascular integrity [47]. Interventions such as SGLT2 inhibitors

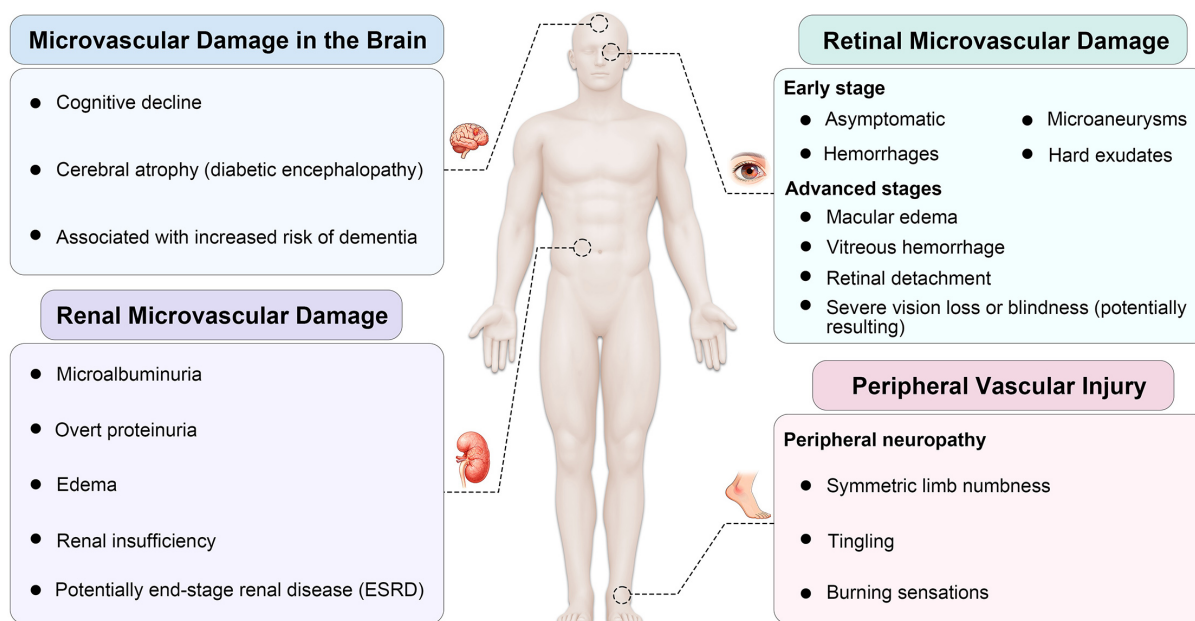


Fig. 2. Clinical consequences of diabetic microvascular complications.

and antioxidants targeting mitochondrial ROS have shown potential in improving cardiac outcomes [48].

Collectively, oxidative stress is a unifying mechanism across diabetic nephropathy, retinopathy, and cardiovascular microvascular dysfunction. However, the downstream pathways and therapeutic targets exhibit organ-specific differences. Oxidative stress in organ-specific microvascular complications of diabetes and treatment strategies were summarized in Fig. 3.

7. Therapeutic Strategies

7.1 Pharmacotherapy

The treatment and management strategies for diabetes have improved significantly, with the overall mortality rate due to this disease falling by approximately one-third over the past 20 years [49]. T1DM relies primarily on insulin therapy, with the optimal injection sites for insulin absorption being subcutaneous tissue of the abdomen, buttocks, thighs, and upper arms. The Professional Practice Committee of the American Diabetes Association recommends treating most adult T1DM patients using continuous subcutaneous insulin infusion, or multiple daily injections of prandial insulin (either by injection or inhalation) along with basal insulin [50]. HbA1c reflects the average blood glucose concentration over the preceding 2–3 months. It quantifies the glycation of hemoglobin and serves as a critical biomarker for evaluating long-term glycemic control in diabetes management [51]. The Diabetes Control and Complications Trial (DCCT) found that this recommended intensive therapy could reduce HbA1c levels and significantly decrease the complications of microvascular disease [52,53].

However, high-dose subcutaneous administration of exogenous insulin in patients with T1DM may exacerbate insulin resistance. Furthermore, studies have demonstrated that adjunct therapies such as pramlintide, glucagon-like peptide-1 receptor agonists (GLP-1 RAs), and SGLT2 inhibitors exert clinically significant benefits in terms of glycemic control (as evidenced by A1C reduction), weight management, and blood pressure modulation. These agents also demonstrate potential in reducing the incidence of diabetic microvascular complications [54,55,56].

Metformin hydrochloride, a biguanide, has become a widely used medication for the treatment of T2DM due to its remarkable glucose-lowering efficacy, low cost, moderate evidence of cardioprotection, and absence of hypoglycemia as an adverse effect [57]. It has been classified as an essential medicine for diabetes treatment by the World Health Organization [50]. The cellular and molecular mechanisms that underpin the action of metformin are not yet fully understood. However, it is generally believed that metformin primarily exerts its effects by inhibiting hepatic gluconeogenesis, with contributions from muscle tissue and gut microbiota considered secondary. Hepatic gluconeogenesis is regulated through four distinct mechanisms: transcriptional, allosteric, substrate availability, and redox state, with the primary suppression of gluconeogenesis *in vivo* occurring via redox-dependent reactions [58].

Sulfonylureas have progressed to the third generation and have become a commonly used class of oral hypoglycemic agents. They stimulate pancreatic β -cells to secrete insulin, thereby reducing blood glucose by an average of 1–2% and effectively lowering the risk of microvascular complications. Consequently, sulfonylureas are often considered as an adjunctive treatment to metformin [59].

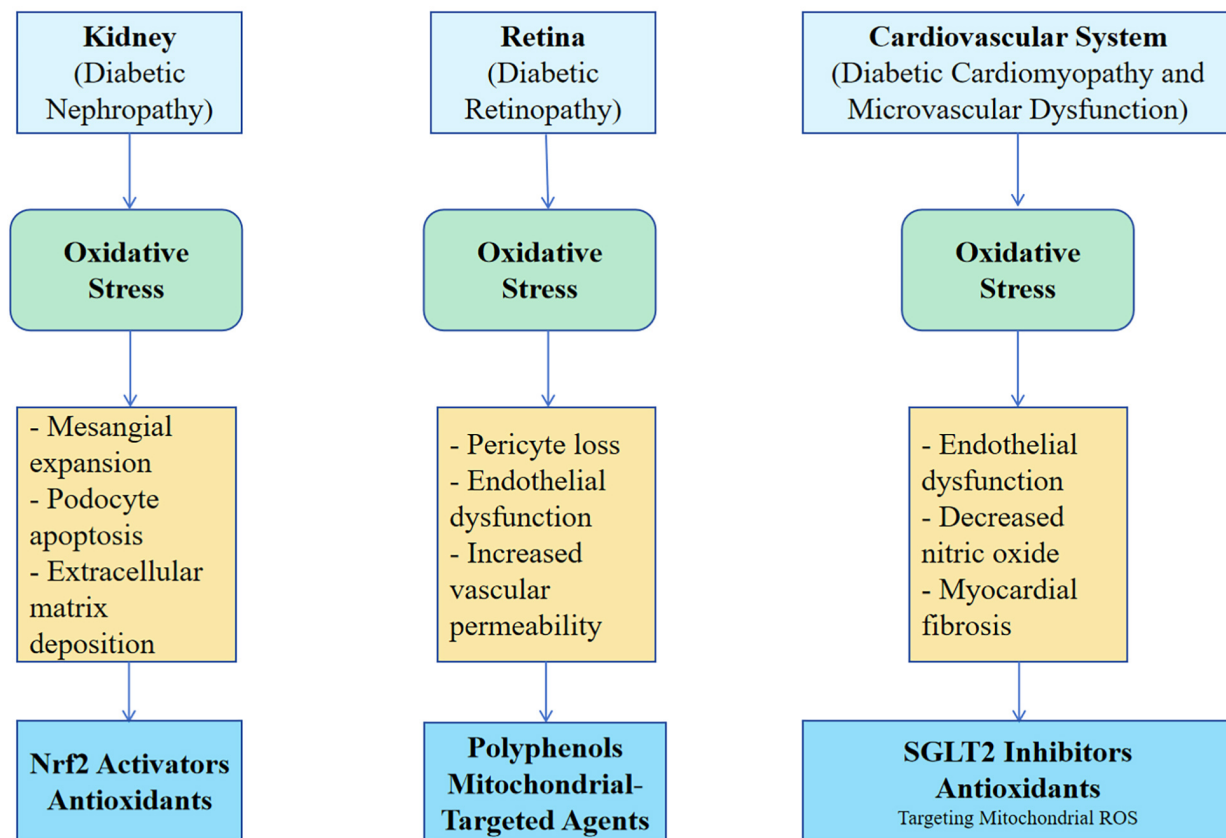


Fig. 3. Oxidative stress in organ-specific microvascular complications of diabetes.

α -Glucosidase inhibitors competitively inhibit α -glucosidase. By delaying glucose absorption in the small intestine, they have a beneficial effect in controlling postprandial hyperglycemia and its harmful physiological complications, particularly in T2DM [60].

Incretin enhancers and analogues include dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like GLP-1RAs, and GLP-1/GIP co-agonists. These exert an “incretin effect”, whereby oral glucose elicits greater insulin secretion than an equivalent intravenous glucose load at the same plasma glucose concentration. This effect is pivotal for glucose homeostasis and in the pathophysiology of T2DM [61,62].

Traditional therapeutic strategies for diabetes have significant limitations. For example, exogenous insulin injection for both T1DM and T2DM can easily provoke severe, potentially life-threatening hypoglycemia when the administered dose is even slightly higher than required [63,64].

Gastrointestinal side effects are common with metformin and may contribute to reduced patient adherence to biguanide therapy [65]. Moreover, metformin can also induce intestinal dysbiosis, as demonstrated by decreased gut microbial diversity in mice. This may be a contributing factor to its gastrointestinal intolerance [66]. Compared with other antidiabetic agents, sulfonylureas increase the risk of

CVD, markedly increase the incidence of hypoglycemic events, accelerate β -cell apoptosis and exhaustion, and impair endothelial function, thereby elevating the risk of ischemic complications [67]. α -glucosidase inhibitors, incretin enhancers, and their analogues frequently provoke adverse gastrointestinal events such as diarrhea and abdominal distension. They can also induce hypoglycemia when co-administered with metformin or sulfonylureas [63].

Oral antidiabetic agents and insulin primarily target the control of glycemic indices, but are unable to halt the ongoing progression of the diabetic pathological process. Contemporary diabetes management has moved beyond simple glucose regulation to include comprehensive health care for the disease itself and its associated complications. Nevertheless, traditional therapeutic approaches fall short of achieving the overarching goals of high-quality, whole-person health management. They still cannot adequately deliver the desired long-term health outcomes, or achieve disease reversal or cure. Consequently, there is an urgent need to develop innovative therapeutic management strategies and diagnostic technologies.

7.2 Adjunctive Therapy

Treatment goals for T2DM include the prevention, delay, and reduction of microvascular complications, while maintaining the patients' quality of life. Achieving these

goals necessitates control of blood glucose levels, management of cardiovascular risk factors, and regular follow-up. Focusing on a patient-centered strategy is crucial for improving patient involvement in self-care practices [68]. Predisposing factors for DM include smoking, obesity, and dyslipidemia. Epidemiological studies have established atherosclerosis as one of the leading causes of mortality among individuals with DM [69]. Therefore, the management of T2DM has shifted from a glucose-centered approach to a more comprehensive therapeutic management strategy [70,71]. The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommend the implementation of strategies that mitigate diabetic complications and improve quality of life. These include: increasing aerobic exercise and resistance training (with intervals ≤ 2 days between sessions); reducing sedentary time; adjusting insulin regimens; modifying carbohydrate intake based on pre-exercise blood glucose levels; and ensuring appropriate foot care during physical activity in individuals with peripheral neuropathy. This comprehensive approach for diabetes management targets metabolic optimization and risk reduction [72]. Adjunctive therapeutic measures such as dietary control and regular exercise have been shown to significantly improve insulin sensitivity and reduce oxidative stress, thereby alleviating microvascular complications. Here we present strategies for carbohydrate intake and exercise intensity based on pre-exercise blood glucose levels (adapted from [73]).

7.3 Gene Therapy

Gene therapy can prevent disease onset or halt its progression by delivering or manipulating genetic material into cells to target the defective gene responsible for disease development and correct the underlying molecular defect [43,74]. By targeting the key pathological mechanisms of diabetic microvascular complications, such as oxidative stress and endothelial injury, gene therapy holds promise for addressing vascular damage. Indeed, gene therapy has emerged as a potential therapeutic alternative in the treatment of T1DM. Common approaches include the overexpression of genes and proteins implicated in T1DM, transplantation of cells engineered to express T1DM-related genes, genetic vaccines, and gene-based immunomodulatory interventions. These strategies are still under investigation, and their safety profiles require further validation [75]. Gene therapy has also demonstrated potential for correcting T2DM and insulin resistance. Encouraging results have been reported from studies in animal models with *FGF21* gene therapy, plasmid-based delivery of adiponectin, and glucagon-like peptide-1 (*GLP-1*) gene therapy, underscoring their potential for the treatment of obesity and insulin resistance. However, these approaches have not yet advanced to clinical application [76,77]. Studies have found that specific circular RNAs may regulate the expression of the Metallothionein 2A gene (*MT2A* gene) by adsorbing miRNAs.

This induces apoptosis in pancreatic β -cells and modulates the expression of diabetes-related genes, thereby contributing to the development of diabetes and providing a new perspective for regulatory therapies involving gene expression in DM [78,79].

CRISPR/Cas9 technology can be used to develop drug testing models and to identify and correct genetic defects. This technology enables precise repair or knockout of gene mutations associated with diabetic microvascular complications, thereby optimizing diabetes treatment. However, the delivery technology for CRISPR systems in humans is still immature and faces challenges such as immune rejection and high off-target rates [80,81]. Therefore, while CRISPR/Cas9 technology is a very effective gene editing tool, more progress is required before it can be applied clinically [74,82].

Gene therapy holds great promise by addressing the root causes of disease at the molecular level. However, due to the associated technical risks, further research and technological advances are needed to pave the way for innovative and potentially curative treatments.

7.4 Stem Cell Treatment

Stem cell therapy is an evolving treatment strategy. MSCs protect microvessels by releasing anti-inflammatory substances, such as IL-10 and TGF- β , as well as pro-angiogenic factors, including VEGF and FGF. Additionally, MSCs have the capacity to differentiate into ECs and pericytes, thereby directly promoting vascular reconstruction. Endothelial stem cells (ESCs) and induced pluripotent stem cells (iPSCs) are capable of progressively differentiating into pancreatic progenitor cells and insulin-producing cells [83]. Endothelial progenitor cells (EPCs) can migrate to sites of vascular injury, differentiate into ECs, and promote angiogenesis, while improving the local microenvironment through paracrine mechanisms. On the other hand, iPSCs can differentiate into retinal cells, glomerular cells, or neuronal cells to replace damaged tissues. The co-transplantation of retinal progenitor cells (RPCs) and MSCs was reported to significantly improve retinal vascular leakage and inflammatory responses in diabetic mouse models [84]. Furthermore, the derivation of pancreatic β -cells from stem cell transplantation offers a novel therapeutic direction. VX-880 stem cells have been successfully differentiated into islet cells, effectively restoring insulin secretion function in patients and showing a high level of safety [85]. Immature neonatal porcine islets (insulin-producing cell source) combined with blood-outgrowth ECs from healthy donors have been used to construct a functional, xenogeneic vascularized endocrine pancreas (VEP) [86]. Researchers have also decellularized lungs and repurposed them to construct a VEP from human iPS cells (iVEP), thereby overcoming the limitations of intrahepatic islet transplantation in T1DM [87]. Stem-cell therapy aims to restore physiological insulin secretion by regenerating functional β -cells

or promoting endogenous β -cell renewal, thereby reversing β -cell failure and preventing the onset of diabetes and its complications. Although this approach shows considerable therapeutic promise, challenges such as immune rejection remain. Future integration with gene-therapy technologies is expected to overcome this hurdle.

8. Perspectives

8.1 Pathogenic Mechanisms

The development and progression of diabetic microvascular complications is affected by multiple pathological mechanisms, including oxidative stress, inflammatory responses, endothelial dysfunction, and the buildup of AGEs. Although some studies have explored these mechanisms in depth, many aspects remain to be elucidated. For instance, the specific molecular mechanisms underlying diabetic microvascular damage are not yet fully understood. It is crucial to determine more precisely how diabetes damages ECs, VSMCs, neurons, and renal cells, as well as the interactions among different cell types [88,89]. With ongoing advances in genomics, proteomics, and metabolomics, future research should employ multidisciplinary approaches to shed light on the mechanisms of diabetic microvascular damage. Additionally, there is considerable heterogeneity among diabetic patients, with significant variability in disease progression and the occurrence of complications [90]. Researchers often fail to consider individual differences, particularly with regard to how genetic, environmental, and lifestyle factors collectively influence microvascular damage [91]. Therefore, future studies should focus on differences between various populations and individuals, and on potential factors that may impact the development of diabetic microvascular complications.

8.2 Personalized Therapeutic Approaches

Personalized treatment is a critical aspect of diabetes management that cannot be overlooked. To obtain a better understanding of diabetic microvascular complications, future research should pay close attention to how individual patient differences affect treatment outcomes [64]. Currently, most treatment approaches employ a “one-size-fits-all” standardized protocol, which often cannot be adjusted according to the patients’ specific circumstances [92]. Personalized treatment strategies can be optimized in the following areas.

Precise Diagnosis and Assessment: Customize personalized treatment plans by utilizing high-throughput technologies such as genomics, proteomics, and metabolomics, in combination with information on individual genetic backgrounds, environmental factors, and disease types. This approach not only enhances therapeutic efficacy, but also effectively avoids unnecessary side effects.

Personalized Pharmacotherapy: Different patients exhibit varied responses to medications, and the role of individual differences in diabetic drug efficacy urgently needs

further exploration. Through pharmacogenomics and pharmacokinetic research, personalized pharmacological regimens can be provided for each patient, minimizing adverse reactions and maximizing therapeutic effectiveness.

Assessment of Long-term Efficacy and Safety: All new treatment methods and medications must undergo rigorous clinical trials to evaluate their long-term efficacy and safety. The management of diabetic microvascular complications often requires prolonged intervention, making it essential to assess the long-term effects of treatments.

9. Conclusions

The development of diabetic microvascular complications is intricate and encompasses various pathophysiological processes. Chronic hyperglycemia is the central driving factor of microvascular damage, leading to abnormalities in microvascular structure and function through various pathways, including the induction of oxidative stress, inflammatory responses, protein glycation, and hemodynamic changes. The buildup of AGEs, overactivation of PKC isoforms, and the stimulation of the hexosamine and polyol pathways lead to an increase in ROS. This intensifies oxidative stress and causes dysfunction in ECs, ultimately initiating microvascular complications.

Recent research on the mechanisms of diabetic microvascular damage has provided directions for developing new therapeutic strategies, such as antioxidants, anti-inflammatory agents, gene therapy, and stem cell therapy. Future studies should focus on exploring individualized treatment strategies and elucidate the molecular mechanisms of diabetic microvascular damage, aiming to develop more precise therapeutic approaches.

Abbreviations

AGEs, advanced glycation end products; ROS, reactive oxygen species; PARP, poly (ADP-ribose) polymerase; GSSG, glutathione disulfide; PKC, protein kinase C; T1DM, type 1 diabetes; T2DM, type 2 diabetes; GDM, gestational diabetes; NDM, neonatal diabetes; BM, basement membrane; WMHs, white matter hyperintensities; ART, ADP-ribosyltransferase; PAR, (MAR) or poly (ADP-ribose); DDR, DNA damage response; DAMPs, damage-associated molecular patterns; mtDNA, mitochondrial DNA; AMPK, AMP-activated protein kinase; TFAM, mitochondrial transcription factor A; PTMs, post-translational modifications; NF- κ B, nuclear factor kappa-B; IRS-1, insulin receptor substrate-1; DAG, Diacylglycerol; NADPH, nicotinamide adenine dinucleotide phosphate; DHAP, dihydroxyacetone phosphate; VEGF, Vascular Endothelial Growth Factor; eNOS, endothelial nitric oxide synthase; mRNA, messenger RNA; HBP, hexosamine biosynthetic pathway; UDP-GlcNAc, uridine diphosphate N-acetylglucosamine; OGT, O-GlcNAc transferase; OGA, O-GlcNAcase; GFAT, glutamine, fructose-6-phosphate amidotransferase; AR, aldose reductase; SDH, sorbitol

dehydrogenase; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; MGO, methylglyoxal; F-6-P, fructose-6-phosphate; O-GlcNAc, O-linked N-acetylglucosamine; NOX, NADPH oxidase; ARE, antioxidant response element; GPX, glutathione peroxidase; SIRT1, silent mating type information regulation 2 homolog-1; LKB1, liver kinase B1; ATP, adenosine triphosphate; DKD, diabetic kidney disease; OCT, optical coherence tomography; DR, Diabetic retinopathy; DPN, Diabetic peripheral neuropathy; HbA1c, glycated hemoglobin; SCS, spinal cord stimulation; ESRD, end-stage renal disease; Nrf1, nuclear factor erythroid 2-related factor 1; Nrf2, nuclear factor erythroid 2-related factor 2; SGLT2, sodium-glucose cotransporter 2; GLP-1 RAs, glucagon-like peptide-1 receptor agonists; DCCT, Diabetes Control and Complications Trial; DPP-4, dipeptidyl peptidase-4; EASD, European Association for the Study of Diabetes; ADA, American Diabetes Association; GSH, intracellular glutathione; MT2A gene, Metallothionein 2A gene; ESCs, Endothelial stem cells; iPSCs, induced pluripotent stem cells; EPCs, Endothelial progenitor cells; RPCs, retinal progenitor cells; VEP, vascularized endocrine pancreas; RAGE, receptor for Advanced Glycation End Products; HO-1, heme oxygenase-1; NQO1, NAD(P)H quinone oxidoreductase 1; GCLC/GCLM, glutamate-cysteine ligase; SOD, superoxide dismutase; CAT, catalase; PGC-1 α , peroxisome proliferator-activated receptor gamma coactivator 1- α .

Author Contributions

JX, WW and SC conceived and designed this review. JX, WW contributed to the writing of the manuscript. JP and YW participated in designing the research study. YW and HZ participated in making figures and searching references. JP, YW and HZ were involved in reviewing the manuscript critically for important intellectual content. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This study is supported by the National Natural Science Foundation of China (grant number: 82500581), and Zhongnan Hospital of Wuhan University (grant number: ZNYQ2023002).

Conflicts of Interest

The authors declare no conflicts of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the authors used ChatGpt (GPT-4.5, OpenAI, San Francisco, California, USA) and DeepSeek (DeepSeek-R1, DeepSeek Inc, Hangzhou, Zhejiang, China) to check spelling and grammar. After using these AI tools, the authors reviewed and edited the full text as needed and take full responsibility for the content of the manuscript.

References

- [1] Xu Y, Lu J, Li M, Wang T, Wang K, Cao Q, et al. Diabetes in China part 1: epidemiology and risk factors. *The Lancet Public Health*. 2024; 9: e1089–e1097. [https://doi.org/10.1016/s2468-2667\(24\)00250-0](https://doi.org/10.1016/s2468-2667(24)00250-0)
- [2] NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in diabetes prevalence and treatment from 1990 to 2022: a pooled analysis of 1108 population-representative studies with 141 million participants. *Lancet* (London, England). 2024; 404: 2077–2093. [https://doi.org/10.1016/S0140-6736\(24\)02317-1](https://doi.org/10.1016/S0140-6736(24)02317-1)
- [3] American Diabetes Association Professional Practice Committee. 2. Diagnosis and Classification of Diabetes: Standards of Care in Diabetes-2025. *Diabetes Care*. 2025; 48: S27–S49. <https://doi.org/10.2337/dc25-s002>.
- [4] Mimura T, Noma H. Oxidative Stress in Diabetic Retinopathy: A Comprehensive Review of Mechanisms, Biomarkers, and Therapeutic Perspectives. *Antioxidants* (Basel, Switzerland). 2025; 14: 1204. <https://doi.org/10.3390/antiox14101204>
- [5] American Diabetes Association Professional Practice Committee. 2. Diagnosis and Classification of Diabetes: Standards of Care in Diabetes-2024. *Diabetes Care*. 2024; 47: S20–S42. <https://doi.org/10.2337/dc24-s002>.
- [6] Pleus S, Tytko A, Landgraf R, Heinemann L, Werner C, Müller-Wieland D, et al. Definition, Classification, Diagnosis and Differential Diagnosis of Diabetes Mellitus: Update 2023. *Experimental and Clinical Endocrinology & Diabetes*. 2024; 132: 112–124. <https://doi.org/10.1055/a-2166-6643>
- [7] DiMeglio LA, Evans-Molina C, Oram RA. Type 1 diabetes. *The Lancet*. 2018; 391: 2449–2462. [https://doi.org/10.1016/s0140-6736\(18\)31320-5](https://doi.org/10.1016/s0140-6736(18)31320-5)
- [8] Quattrin T, Mastrandrea LD, Walker LSK. Type 1 diabetes. *Lancet* (London, England). 2023; 401: 2149–2162. [https://doi.org/10.1016/S0140-6736\(23\)00223-4](https://doi.org/10.1016/S0140-6736(23)00223-4)
- [9] Skowera A, Ladell K, McLaren JE, Dolton G, Matthews KK, Gostick E, et al. β -Cell-Specific CD8 T Cell Phenotype in Type 1 Diabetes Reflects Chronic Autoantigen Exposure. *Diabetes*. 2014; 64: 916–925. <https://doi.org/10.2337/db14-0332>
- [10] Herold KC, Delong T, Perdigoto AL, Biru N, Brusko TM, Walker LSK. The immunology of type 1 diabetes. *Nature Reviews. Immunology*. 2024; 24: 435–451. <https://doi.org/10.1038/s41577-023-00985-4>
- [11] Li Y, Du Y, Liu Y, Chen X, Li X, Duan Y, et al. Cardiomyocyte-derived small extracellular vesicle: a new mechanism driving diabetic cardiac fibrosis and cardiomyopathy. *Theranostics*. 2024; 14: 5926–5944. <https://doi.org/10.7150/thno.99507>
- [12] Guven G, Hilty MP, Ince C. Microcirculation: Physiology, Pathophysiology, and Clinical Application. *Blood Purification*. 2020; 49: 143–150. <https://doi.org/10.1159/000503775>.
- [13] Lyssenko V, Vaag A. Genetics of diabetes-associated microvascular complications. *Diabetologia*. 2023; 66: 1601–1613. <https://doi.org/10.1007/s00125-023-05964-x>
- [14] Horton WB, Barrett EJ. Microvascular Dysfunction in Diabetes Mellitus and Cardiometabolic Disease. *Endocrine Reviews*.

- 2021; 42: 29–55. <https://doi.org/10.1210/endrev/bnaa025>
- [15] Donthula G, Daigavane S. Diabetes Mellitus and Neurovascular Pathology: A Comprehensive Review of Retinal and Brain Lesions. *Cureus*. 2024; 16: e70611. <https://doi.org/10.7759/cureus.70611>
 - [16] Liu Y, Zhang H, Wang S, Guo Y, Fang X, Zheng B, et al. Reduced pericyte and tight junction coverage in old diabetic rats are associated with hyperglycemia-induced cerebrovascular pericyte dysfunction. *American Journal of Physiology. Heart and Circulatory Physiology*. 2021; 320: H549–H562. <https://doi.org/10.1152/ajpheart.00726.2020>
 - [17] Roy B. Pathophysiological Mechanisms of Diabetes-Induced Macrovascular and Microvascular Complications: The Role of Oxidative Stress. *Medical Sciences (Basel, Switzerland)*. 2025; 13: 87. <https://doi.org/10.3390/medsci13030087>
 - [18] Low Wang CC, Hess CN, Hiatt WR, Goldfine AB. Clinical Update: Cardiovascular Disease in Diabetes Mellitus: Atherosclerotic Cardiovascular Disease and Heart Failure in Type 2 Diabetes Mellitus - Mechanisms, Management, and Clinical Considerations. *Circulation*. 2016; 133: 2459–2502. <https://doi.org/10.1161/circulationaha.116.022194>
 - [19] Wang W, Lo ACY. Diabetic Retinopathy: Pathophysiology and Treatments. *International Journal of Molecular Sciences*. 2018; 19: 1816. <https://doi.org/10.3390/ijms19061816>
 - [20] Jellinger KA. Pathomechanisms of Vascular Depression in Older Adults. *International Journal of Molecular Sciences*. 2021; 23: 308. <https://doi.org/10.3390/ijms23010308>
 - [21] Li Y, Liu Y, Liu S, Gao M, Wang W, Chen K, et al. Diabetic vascular diseases: molecular mechanisms and therapeutic strategies. *Signal Transduction and Targeted Therapy*. 2023; 8. <https://doi.org/10.1038/s41392-023-01400-z>
 - [22] Wimmer RA, Leopoldi A, Aichinger M, Wick N, Hantusch B, Novatchkova M, et al. Human blood vessel organoids as a model of diabetic vasculopathy. *Nature*. 2019; 565: 505–510. <https://doi.org/10.1038/s41586-018-0858-8>
 - [23] Marassi M, Fadini GP. The cardio-renal-metabolic connection: a review of the evidence. *Cardiovascular Diabetology*. 2023; 22: 195. <https://doi.org/10.1186/s12933-023-01937-x>
 - [24] Tan SM, de Haan JB. Combating oxidative stress in diabetic complications with Nrf2 activators: how much is too much? *Redox Rep*. 2014; 19: 107–117. <https://doi.org/10.1179/1351000214Y.00000000087>
 - [25] Kirkman DL, Robinson AT, Rossman MJ, Seals DR, Edwards DG. Mitochondrial contributions to vascular endothelial dysfunction, arterial stiffness, and cardiovascular diseases. *American journal of physiology. Heart and circulatory physiology*. 2021; 320: H2080–H2100. <https://doi.org/10.1152/ajpheart.00917.2020>
 - [26] Khalid M, Petroianu G, Adem A. Advanced Glycation End Products and Diabetes Mellitus: Mechanisms and Perspectives. *Biomolecules*. 2022; 12: 542. <https://doi.org/10.3390/biom12040542>
 - [27] Bansal S, Burman A, Tripathi AK. Advanced glycation end products: Key mediator and therapeutic target of cardiovascular complications in diabetes. *World Journal of Diabetes*. 2023; 14: 1146–1162. <https://doi.org/10.4239/wjd.v14.i8.1146>
 - [28] Hayashi D, Shirai Y. The Role of Diacylglycerol Kinase in the Amelioration of Diabetic Nephropathy. *Molecules (Basel, Switzerland)*. 2022; 27: 6784. <https://doi.org/10.3390/molecule27206784>
 - [29] Yamaguchi J, Canaud G. Vascular endothelial growth factor backfiltration in the glomerulus: an intriguing mechanism. *Nephrology, Dialysis, Transplantation : Official Publication of the European Dialysis and Transplant Association - European Renal Association*. 2018; 33: 1483–1484. <https://doi.org/10.1093/ndt/gfy114>
 - [30] Lei Y, Liu Q, Chen B, Wu F, Li Y, Dong X, et al. Protein O-GlcNAcylation coupled to Hippo signaling drives vascular dysfunction in diabetic retinopathy. *Nature Communications*. 2024; 15: 9334. <https://doi.org/10.1038/s41467-024-53601-x>
 - [31] Giacco F, Brownlee M. Oxidative stress and diabetic complications. *Circulation Research*. 2010; 107: 1058–1070. <https://doi.org/10.1161/CIRCRESAHA.110.223545>
 - [32] Thorne CA, Grey AC, Lim JC, Donaldson PJ. The Synergistic Effects of Polyol Pathway-Induced Oxidative and Osmotic Stress in the Aetiology of Diabetic Cataracts. *International Journal of Molecular Sciences*. 2024; 25: 9042. <https://doi.org/10.3390/ijms25169042>
 - [33] Barrett EJ, Liu Z, Khamaisi M, King GL, Klein R, Klein BEK, et al. Diabetic Microvascular Disease: An Endocrine Society Scientific Statement. *The Journal of Clinical Endocrinology and Metabolism*. 2017; 102: 4343–4410. <https://doi.org/10.1210/jc.2017-01922>
 - [34] Jain K, Mottl AK. Comprehensive Care for People With Diabetic Kidney Disease. *Diabetes Spectrum : a Publication of the American Diabetes Association*. 2015; 28: 187–192. <https://doi.org/10.2337/diaspect.28.3.187>
 - [35] Tuttle KR, Agarwal R, Alpers CE, Bakris GL, Brosius FC, Kolkhof P, et al. Molecular mechanisms and therapeutic targets for diabetic kidney disease. *Kidney International*. 2022; 102: 248–260. <https://doi.org/10.1016/j.kint.2022.05.012>
 - [36] Cleveland KH, Schnellmann RG. Pharmacological Targeting of Mitochondria in Diabetic Kidney Disease. *Pharmacological Reviews*. 2023; 75: 250–262. <https://doi.org/10.1124/pharmrev.122.000560>
 - [37] Cioana M, Deng J, Nadarajah A, Hou M, Qiu Y, Chen SSJ, et al. Global Prevalence of Diabetic Retinopathy in Pediatric Type 2 Diabetes: A Systematic Review and Meta-analysis. *JAMA Network Open*. 2023; 6: e231887. <https://doi.org/10.1001/jamanetworkopen.2023.1887>
 - [38] Tan TE, Wong TY. Diabetic retinopathy: Looking forward to 2030. *Frontiers in Endocrinology*. 2023; 13: 1077669. <https://doi.org/10.3389/fendo.2022.1077669>
 - [39] Liu X, Xu Y, An M, Zeng Q. The risk factors for diabetic peripheral neuropathy: A meta-analysis. *PloS One*. 2019; 14: e0212574. <https://doi.org/10.1371/journal.pone.0212574>
 - [40] Petersen EA, Stauss TG, Scowcroft JA, Brooks ES, White JL, Sills SM, et al. Effect of High-frequency (10-kHz) Spinal Cord Stimulation in Patients With Painful Diabetic Neuropathy. *JAMA Neurology*. 2021; 78: 687. <https://doi.org/10.1001/jama.neuro.2021.0538>
 - [41] Seyedizadeh SH, Cheragh-Birjandi S, Hamedia Nia MR. The Effects of Combined Exercise Training (Resistance-Aerobic) on Serum Kinesin and Physical Function in Type 2 Diabetes Patients with Diabetic Peripheral Neuropathy (Randomized Controlled Trials). *Journal of Diabetes Research*. 2020; 2020: 6978128. <https://doi.org/10.1155/2020/6978128>
 - [42] Fakhruddin S, Alanazi W, Jackson KE. Diabetes-Induced Reactive Oxygen Species: Mechanism of Their Generation and Role in Renal Injury. *Journal of diabetes research*. 2017; 2017: 8379327. <https://doi.org/10.1155/2017/8379327>
 - [43] Forbes JM, Cooper ME. Mechanisms of diabetic complications. *Physiological Reviews*. 2013; 93: 137–188. <https://doi.org/10.1152/physrev.00045.2011>
 - [44] Tanase DM, Gosav EM, Anton MI, Floria M, Seritean Isac PN, Hurjui LL, et al. Oxidative Stress and NRF2/KEAP1/ARE Pathway in Diabetic Kidney Disease (DKD): New Perspectives. *Biomolecules*. 2022; 12: 1227. <https://doi.org/10.3390/biom12091227>
 - [45] Kang Q, Yang C. Oxidative stress and diabetic retinopathy: Molecular mechanisms, pathogenetic role and therapeutic implications. *Redox Biology*. 2020; 37: 101799. <https://doi.org/10.1016/j.redox.2020.101799>

- [46] Shinn LJ, Lagalwar S. Treating Neurodegenerative Disease with Antioxidants: Efficacy of the Bioactive Phenol Resveratrol and Mitochondrial-Targeted MitoQ and SkQ. *Antioxidants* (Basel, Switzerland). 2021; 10: 573. <https://doi.org/10.3390/antiox10040573>
- [47] Bugger H, Abel ED. Molecular mechanisms of diabetic cardiomyopathy. *Diabetologia*. 2014; 57: 660–671. <https://doi.org/10.1007/s00125-014-3171-6>
- [48] Packer M. SGLT2 Inhibitors Produce Cardiorenal Benefits by Promoting Adaptive Cellular Reprogramming to Induce a State of Fasting Mimicry: A Paradigm Shift in Understanding Their Mechanism of Action. *Diabetes Care*. 2020; 43: 508–511. <https://doi.org/10.2337/dci19-0074>
- [49] Janić M, Janež A, El-Tanani M, Maggio V, Rizzo M. Diabetes: Recent Advances and Future Perspectives. *Biomedicines*. 2024; 12: 2875. <https://doi.org/10.3390/biomedicines12122875>
- [50] American Diabetes Association Professional Practice Committee. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes-2024. *Diabetes Care*. 2024; 47: S158–S178. <https://doi.org/10.2337/dc24-s009>
- [51] Eyth E, Zubair M, Naik R. Hemoglobin A1C. In: StatPearls [Internet]. StatPearls Publishing: Treasure Island (FL). 2025.
- [52] Lachin JM, Bebu I, Nathan DM, DCCT/EDIC Research Group. The Beneficial Effects of Earlier Versus Later Implementation of Intensive Therapy in Type 1 Diabetes. *Diabetes Care*. 2021; 44: dc211331. <https://doi.org/10.2337/dc21-1331>
- [53] Lachin JM, Nathan DM, DCCT/EDIC Research Group. Understanding Metabolic Memory: The Prolonged Influence of Glycemia During the Diabetes Control and Complications Trial (DCCT) on Future Risks of Complications During the Study of the Epidemiology of Diabetes Interventions and Complications (EDIC). *Diabetes Care*. 2021; 44: dc203097. <https://doi.org/10.2337/dc20-3097>
- [54] Qiao YC, Ling W, Pan YH, Chen YL, Zhou D, Huang YM, et al. Efficacy and safety of pramlintide injection adjunct to insulin therapy in patients with type 1 diabetes mellitus: a systematic review and meta-analysis. *Oncotarget*. 2017; 8: 66504–66515. <https://doi.org/10.18632/oncotarget.16008>
- [55] Rao L, Ren C, Luo S, Huang C, Li X. Sodium-glucose cotransporter 2 inhibitors as an add-on therapy to insulin for type 1 diabetes mellitus: Meta-analysis of randomized controlled trials. *Acta Diabetologica*. 2021; 58: 869–880. <https://doi.org/10.1007/s00592-021-01686-x>
- [56] Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *New England Journal of Medicine*. 2015; 373: 2117–2128. <https://doi.org/10.1056/nejmoa1504720>
- [57] Inzucchi S, Bergenstal R, Buse J, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2015; 38: 140–149. <https://doi.org/10.2337/dc14-2441>
- [58] LaMoia TE, Shulman GI. Cellular and Molecular Mechanisms of Metformin Action. *Endocrine Reviews*. 2021; 42: 77–96. <https://doi.org/10.1210/edrev/bnaa023>
- [59] Lv W, Wang X, Xu Q, Lu W. Mechanisms and Characteristics of Sulfonylureas and Glinides. *Current Topics in Medicinal Chemistry*. 2020; 20: 37–56. <https://doi.org/10.2174/1568026620666191224141617>
- [60] Hossain U, Das AK, Ghosh S, Sil PC. An overview on the role of bioactive α -glucosidase inhibitors in ameliorating diabetic complications. *Food and Chemical Toxicology : an International Journal Published for the British Industrial Biological Research Association*. 2020; 145: 111738. <https://doi.org/10.1016/j.fct.2020.111738>
- [61] Zarei M, Sahebi Vaighan N, Farjoo MH, Talebi S, Zarei M. Incretin-based therapy: a new horizon in diabetes management. *Journal of Diabetes and Metabolic Disorders*. 2024; 23: 1665–1686. <https://doi.org/10.1007/s40200-024-01479-3>
- [62] Hemmingsen B, Sonne DP, Metzendorf MI, Richter B. Dipeptidyl-peptidase (DPP)-4 inhibitors and glucagon-like peptide (GLP)-1 analogues for prevention or delay of type 2 diabetes mellitus and its associated complications in people at increased risk for the development of type 2 diabetes mellitus. *The Cochrane Database of Systematic Reviews*. 2017; 5: CD012204. <https://doi.org/10.1002/14651858.CD012204.pub2>
- [63] Sun Y, Tao Q, Wu X, Zhang L, Liu Q, Wang L. The Utility of Exosomes in Diagnosis and Therapy of Diabetes Mellitus and Associated Complications. *Frontiers in Endocrinology*. 2021; 12: 756581. <https://doi.org/10.3389/fendo.2021.756581>
- [64] Hoeg-Jensen T, Kruse T, Brand CL, Sturis J, Fledelius C, Nielsen PK, et al. Glucose-sensitive insulin with attenuation of hypoglycaemia. *Nature*. 2024; 634: 944–951. <https://doi.org/10.1038/s41586-024-08042-3>
- [65] Triggler CR, Mohammed I, Bshesh K, Marei I, Ye K, Ding H, et al. Metformin: Is it a drug for all reasons and diseases? *Metabolism: Clinical and Experimental*. 2022; 133: 155223. <https://doi.org/10.1016/j.metabol.2022.155223>
- [66] McCreight LJ, Bailey CJ, Pearson ER. Metformin and the gastrointestinal tract. *Diabetologia*. 2016; 59: 426–435. <https://doi.org/10.1007/s00125-015-3844-9>
- [67] Grunberger G. Should Side Effects Influence the Selection of Antidiabetic Therapies in Type 2 Diabetes? *Current Diabetes Reports*. 2017; 17: 21. <https://doi.org/10.1007/s11892-017-0853-8>
- [68] Rodriguez-Gutierrez R, Gionfriddo MR, Ospina NS, Maraka S, Tamhane S, Montori VM, et al. Shared decision making in endocrinology: present and future directions. *The Lancet. Diabetes & Endocrinology*. 2016; 4: 706–716. [https://doi.org/10.1016/S2213-8587\(15\)00468-4](https://doi.org/10.1016/S2213-8587(15)00468-4)
- [69] American Diabetes Association. 9. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes-2018. *Diabetes Care*. 2018; 41: S86–S104. <https://doi.org/10.2337/dc18-s009>
- [70] Aloke C, Ekwu CO, Aja PM, Obasi NA, Chukwu J, Akumadu BO, et al. Current Advances in the Management of Diabetes Mellitus. *Biomedicines*. 2022; 10: 2436. <https://doi.org/10.3390/biomedicines10102436>
- [71] Seetharaman R, Monteiro R, Maradia J, Tripathi R. IcoSema: unveiling the future of diabetes management from a clinical pharmacology perspective. *Journal of Basic and Clinical Physiology and Pharmacology*. 2024; 35: 213–224. <https://doi.org/10.1515/jbcpp-2024-0058>
- [72] Davies MJ, D'Alessio DA, Fradkin J, Kernan WN, Mathieu C, Mingrone G, et al. Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2018; 41: 2669–2701. <https://doi.org/10.2337/dci18-0033>
- [73] Colberg SR, Sigal RJ, Yardley JE, Riddell MC, Dunstan DW, Dempsey PC, et al. Physical Activity/Exercise and Diabetes: A Position Statement of the American Diabetes Association. *Diabetes Care*. 2016; 39: 2065–2079. <https://doi.org/10.2337/dc16-1728>
- [74] Bornstein SR, Wright JF, Steenblock C. The promising potential of gene therapy for diabetes mellitus. *Nature Reviews. Endocrinology*. 2024; 20: 627–628. <https://doi.org/10.1038/s41574-024-01030-7>
- [75] Chellappan DK, Sivam NS, Teoh KX, Leong WP, Fui TZ, Chooi K, et al. Gene therapy and type 1 diabetes mellitus. *Biomedicine*

- & Pharmacotherapy = Biomedecine & Pharmacotherapie. 2018; 108: 1188–1200. <https://doi.org/10.1016/j.biopha.2018.09.138>
- [76] Jimenez V, Jambrina C, Casana E, Sacristan V, Muñoz S, Darriba S, et al. FGF21 gene therapy as treatment for obesity and insulin resistance. *EMBO Molecular Medicine*. 2018; 10: e8791. <https://doi.org/10.15252/emmm.201708791>
- [77] Stafeev YS, Menshikov MY, Parfyonova YV. Gene therapy of type 2 diabetes mellitus: state of art. *Terapevticheskii Arkhiv*. 2019; 91: 149–152. <https://doi.org/10.26442/00403660.2019.02.000042>
- [78] Zhen XJ, Hu RT, Liu NN, Dou JF, Wu T, Zhang YL, et al. CircRNA-mediated ceRNA regulatory networks: transcriptomic insights into obesity type 2 diabetes progression and treatment strategies. *Diabetology & Metabolic Syndrome*. 2025; 17: 57. <https://doi.org/10.1186/s13098-025-01578-y>
- [79] Yuan T, Annamalai K, Naik S, Lupse B, Geravandi S, Pal A, et al. The Hippo kinase LATS2 impairs pancreatic β -cell survival in diabetes through the mTORC1-autophagy axis. *Nature communications*. 2021; 12: 4928. <https://doi.org/10.1038/s41467-021-25145-x>
- [80] Wu K, He M, Mao B, Xing Y, Wei S, Jiang D, et al. Enhanced delivery of CRISPR/Cas9 system based on biomimetic nanoparticles for hepatitis B virus therapy. *Journal of controlled release : official journal of the Controlled Release Society*. 2024; 374: 293–311. <https://doi.org/10.1016/j.jconrel.2024.08.019>
- [81] Du Y, Liu Y, Hu J, Peng X, Liu Z. CRISPR/Cas9 systems: Delivery technologies and biomedical applications. *Asian Journal of Pharmaceutical Sciences*. 2023; 18: 100854. <https://doi.org/10.1016/j.ajps.2023.100854>
- [82] Cheng Y, Wang H, Li M. The promise of CRISPR/Cas9 technology in diabetes mellitus therapy: How gene editing is revolutionizing diabetes research and treatment. *Journal of Diabetes and its Complications*. 2023; 37: 108524. <https://doi.org/10.1016/j.jdiacomp.2023.108524>
- [83] Li H, Zhu H, Ge T, Wang Z, Zhang C. Mesenchymal Stem Cell-Based Therapy for Diabetes Mellitus: Enhancement Strategies and Future Perspectives. *Stem Cell Reviews and Reports*. 2021; 17: 1552–1569. <https://doi.org/10.1007/s12015-021-10139-5>
- [84] Li XJ, Li CY, Bai D, Leng Y. Insights into stem cell therapy for diabetic retinopathy: a bibliometric and visual analysis. *Neural Regeneration Research*. 2021; 16: 172–178. <https://doi.org/10.4103/1673-5374.286974>
- [85] Ramzy A, Thompson DM, Ward-Hartstonge KA, Ivison S, Cook L, Garcia RV, et al. Implanted pluripotent stem-cell-derived pancreatic endoderm cells secrete glucose-responsive C-peptide in patients with type 1 diabetes. *Cell Stem Cell*. 2021; 28: 2047–2061.e5. <https://doi.org/10.1016/j.stem.2021.10.003>
- [86] Citro A, Neroni A, Pignatelli C, Campo F, Policardi M, Monieri M, et al. Directed self-assembly of a xenogeneic vascularized endocrine pancreas for type 1 diabetes. *Nature Communications*. 2023; 14: 878. <https://doi.org/10.1038/s41467-023-36582-1>
- [87] Campo F, Neroni A, Pignatelli C, Pellegrini S, Marzinotto I, Valla L, et al. Bioengineering of a human iPSC-derived vascularized endocrine pancreas for type 1 diabetes. *Cell Reports. Medicine*. 2025; 6: 101938. <https://doi.org/10.1016/j.xcrm.2025.101938>
- [88] Zhu J, Hu Z, Luo Y, Liu Y, Luo W, Du X, et al. Diabetic peripheral neuropathy: pathogenetic mechanisms and treatment. *Frontiers in Endocrinology*. 2024; 14: 1265372. <https://doi.org/10.3389/fendo.2023.1265372>
- [89] Madonna R, Balistreri CR, Geng YJ, De Caterina R. Diabetic microangiopathy: Pathogenetic insights and novel therapeutic approaches. *Vascular Pharmacology*. 2017; 90: 1–7. <https://doi.org/10.1016/j.vph.2017.01.004>
- [90] Ilonen J, Lempainen J, Veijola R. The heterogeneous pathogenesis of type 1 diabetes mellitus. *Nature Reviews. Endocrinology*. 2019; 15: 635–650. <https://doi.org/10.1038/s41574-019-0254-y>
- [91] Tuomi T, Santoro N, Caprio S, Cai M, Weng J, Groop L. The many faces of diabetes: a disease with increasing heterogeneity. *Lancet (London, England)*. 2014; 383: 1084–1094. [https://doi.org/10.1016/S0140-6736\(13\)62219-9](https://doi.org/10.1016/S0140-6736(13)62219-9)
- [92] Elendu C, John Okah M, Fiemotongha KDJ, Adeyemo BI, Bassey BN, Omeludike EK, et al. Comprehensive advancements in the prevention and treatment of diabetic nephropathy: A narrative review. *Medicine*. 2023; 102: e35397. <https://doi.org/10.1097/MD.00000000000035397>