Newly Identified Molecular Mechanisms of Vascular Dysfunction in Diabetes

Mecanismos Moleculares de Disfunção Vascular na Diabetes Recentemente Identificados

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Abstract

Diabetes *mellitus* (DM) is a growing metabolic disorder with long term hyperglycemia as a hallmark. DM is interlinked with micro and macroangiopathy ultimately leading to elevated morbidity and mortality rates in diabetic patients. Indeed, vascular complications associated with diabetes present a substantial risk to human health. Traditional approaches focusing solely on addressing one vascular complication are inadequate for effectively managing diabetes over the long term. Diabetic vascular complications are multifaceted and involve complex mechanisms that contribute to the development of endothelial dysfunction. The molecular mechanisms underlying vascular complications in diabetes involve an intricate interplay between various pathways, including those related to glucose metabolism, oxidative stress, inflammation, endothelial dysfunction, and dyslipidemia. Diabetic vascular disease encompasses a broad clinical spectrum affecting vessels of varying sizes across multiple systems including the heart, brain, kidneys, eyes, and peripheral regions. Pathological presentations commonly include macrovascular atherosclerosis alongside microvascular endothelial dysfunction, thickening of the basement membrane, and thrombosis. Thus, addressing vasculopathy in diabetes requires a comprehensive approach that targets molecular pathways, utilizes pharmacological interventions, implements lifestyle modifications, and focuses on personalized medicine and preventive strategies.

Keywords: diabetes *mellitus*; macroangiopathy; microangiopathy; molecular mechanisms; vascular dysfunction.

Resumo

A diabetes *mellitus* (DM) é uma perturbação metabólica crescente que tem a hiperglicemia de longo prazo como marca distintiva. A DM está interligada com micro e macroangiopatia, levando a taxas elevadas de morbilidade e mortalidade nos doentes diabéticos. Na verdade, as complicações vasculares associadas à diabetes constituem um risco substancial para a saúde humana. As abordagens tradicionais, que se concentram apenas no tratamento de uma complicação vascular, são inadequadas para o controlo eficaz da diabetes a longo prazo. As complicações vasculares da DM são multifacetadas e envolvem mecanismos complexos que contribuem para o desenvolvimento de disfunção endotelial. Na DM, os mecanismos moleculares subjacentes às complicações vasculares envolvem uma interação complexa entre várias vias, incluindo as relacionadas com o metabolismo da glicose, stresse oxidativo, inflamação, disfunção endotelial e dislipidemia. A doença vascular diabética abrange um amplo espectro clínico que afeta vasos de dimensões variadas em vários sistemas, incluindo coração, cérebro, rins, olhos e regiões periféricas. As apresentações patológicas incluem, geralmente, aterosclerose macrovascular juntamente com disfunção endotelial microvascular, espessamento da membrana basal e trombose. Assim, na DM, abordar a vasculopatia requer uma abordagem abrangente que atinja as vias moleculares, utilize intervenções farmacológicas, implemente modificações do estilo de vida e se concentre na medicina personalizada e em estratégias preventivas.

Palavras-chave: diabetes *mellitus*; macroangiopatia; microangiopatia; mecanismos moleculares; disfunção vascular.

> INTRODUCTION

Chronic hyperglycemia and metabolic dysregulation in diabetes mellitus (DM) lead to vascular complications, causing damage and dysfunction in the body's vasculature over time (Giacco, Brownlee, 2010). This dysfunction can manifest in both micro and macrovascular systems, contributing to the morbidity and mortality of diabetic individuals (Harding et al., 2019; Saeedi et al., 2019).

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Diabetic vasculopathy encompasses macroangiopathy and microangiopathy. Macroangiopathy involves atherosclerosis in large and medium arteries (such as the aorta, coronary, renal, basilar, and peripheral arteries), whereas microangiopathy entails endothelial damage in vessels between primary arterioles and venules, thickening of the vascular basement membrane, thrombosis, and aggregation of platelets and red blood cells, along with microcirculatory disorders (Mota et al., 2020). Due to variations in vascular structure, hemodynamics, and affected cell types, macro/microangiopathy present with distinct pathological features (Dal Canto et al., 2019). Atherosclerosis typically occurs in regions with hemodynamic disturbances, particularly in elastic arteries, characterized by macrophage accumulation and endothelial cell lesions, along with smooth muscle cell damage. The narrowing and hardening of arteries due to plaque buildup restricts blood flow, increasing the risk of cardiovascular diseases such as coronary artery disease, stroke, and peripheral artery disease (Figure 1; Lusis, 2000). Small vessels, being more hemodynamically stable with fewer cell layers, exhibit a rich plexus. Moreover, variations in energy metabolism and organ-specific cytokines or growth factors are attributed to various target organs (Zhou et al., 2022). Diabetic microvasculopathy primarily affects the kidney and retina (Figure 2; Avogaro, Fadini, 2019), while diabetic macrovasculopathy affects most target organs, including the heart, brain, and peripheral vasculature (Figure 1; Mota et al., 2020).

Diabetes and its vascular complications involve the dysfunction of various components within the vascular system, including endothelial cells, vascular smooth muscle cells (VSMC), pericytes, and other cell types. Common vascular diseases such as atherosclerosis, endothelial impairment, pericyte loss, capillary thinning, and angiogenesis disorders are widespread. The complex network of blood vessels, nerves, and lymphatic vessels is surrounded by connective tissue membranes forming vascular nerve bundles. Variations in intravascular structures, perivascular tissues, and vascular nerve bundles lead to alterations in vascular function (Queiroz, Sena, 2020). Vascular complications in DM are promoted by imbalances in the metabolism of glucose and lipids, additionally through the stimulation of the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS), which can result in extensive vascular injury everywhere in the body. Hyperglycemia leads to the formation of advanced glycation end products (AGEs), which contribute to endothelial dysfunction, oxidative stress, and inflammation. Dyslipidemia, another common feature of diabetes, leads to the deposition of cholesterol-rich plaques in blood vessels. Additionally, diabetes induces abnormalities in VSMC function, further exacerbating atherosclerosis (Sena et al., 2013; Poznuak et al., 2020). The sympathetic nervous system predominantly triggers vasoconstriction, while the RAAS regulates vascular tone, blood volume, and blood pressure (Jacob et al., 2016; Freeman et al., 2014). Surrounding tissues tightly regulate the vascular systems of target organs, controlling microvascular units through both physical and signal transduction mechanisms (Avogaro, Fadini, 2019). As DM progresses, patients become more susceptible to various vascular complications, including endothelial dysfunction, atherosclerosis, and microcirculatory disorders, which interact and contribute to the development of diabetic vasculopathy (Zhou et al., 2022).

> OVERVIEW OF MOLECULAR MECHANISMS

Diabetes-associated vasculopathy arises from pathophysiological processes such as hyperglycemia and insulin resistance. The molecular mechanisms underlying the vascular complications are multifactorial and involve complex interactions among various cellular pathways. The vascular complications of diabetes result from the interplay of various molecular pathways including oxidative stress, inflammation, endothelial dysfunction, and dysregulated signaling cascades. In addition, immune system activation, dysregulated microRNAs (miRNAs), and the accumulation of AGEs are also involved (Figure 3; Oguntibeju, 2019; Dehghan et al., 2022; Tucker et al., 2023). Targeting these pathways through lifestyle interventions, pharmacotherapy, and glycemic control is crucial for preventing and managing diabetic vascular complications.

Endothelial Dysfunction

Diabetes disrupts endothelial nitric oxide (NO) synthesis and bioavailability by multiple mechanisms, including decreased endothelial nitric oxide synthase activity, increased reactive oxygen species (ROS)-mediated NO degradation, and impaired NO release from endothelial cells (Sena et al., 2008). Reduced NO levels lead to vasoconstriction, inflammation, platelet aggregation, and VSMC proliferation (Sena et al., 2013).

Endothelial dysfunction plays a critical role in the pathogenesis of vasculopathy in diabetes by disrupting vascular homeostasis and promoting inflammation, oxidative stress, and thrombosis.

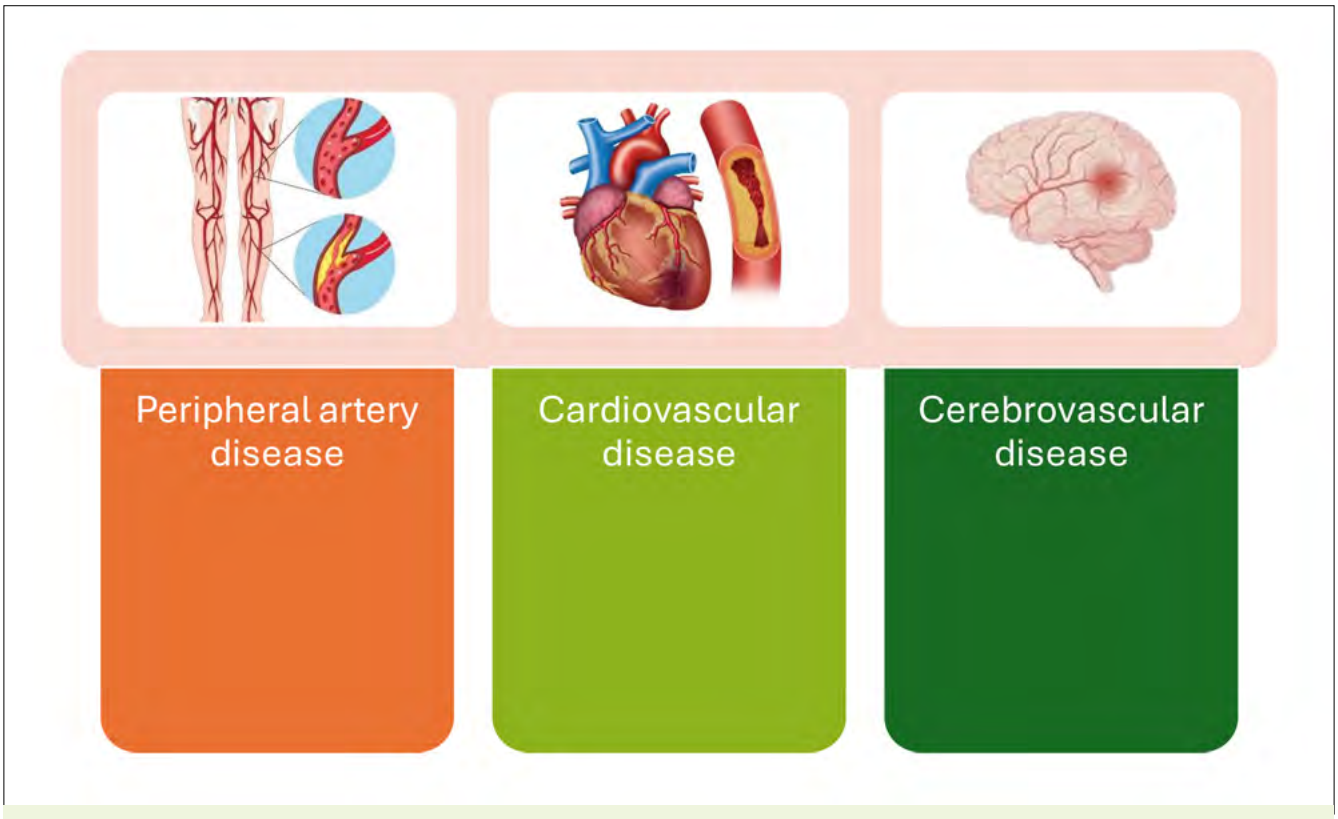

Figure 1 - Macrovascular dysfunction.

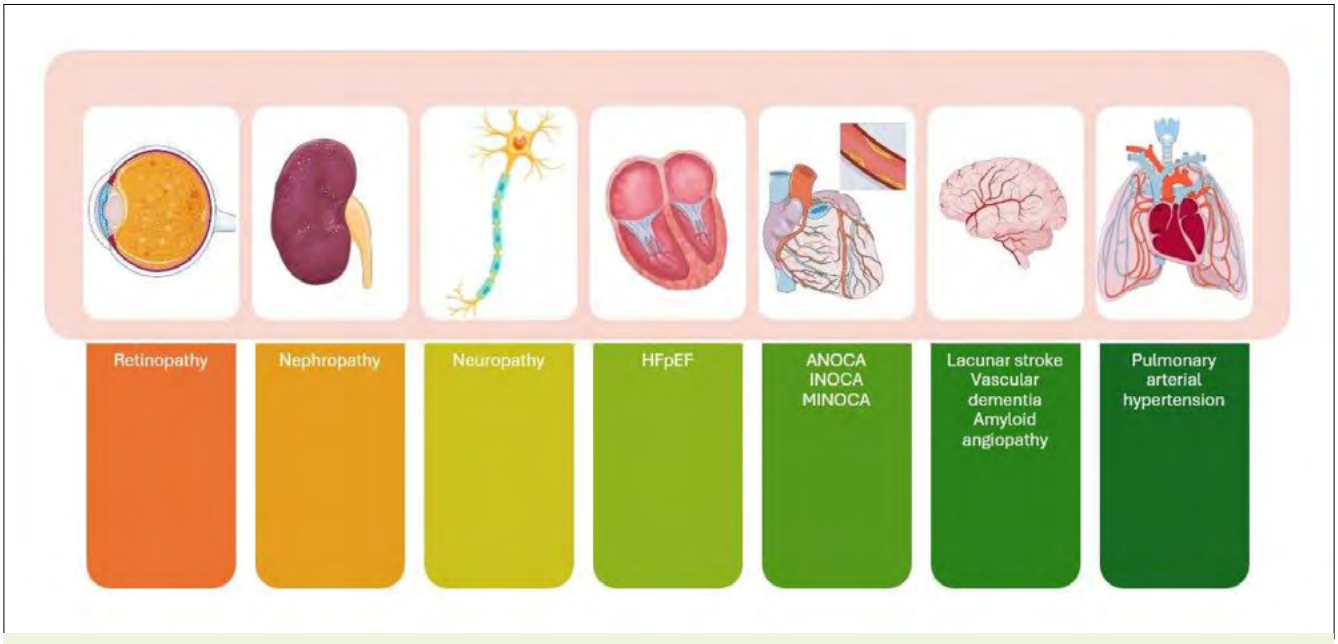

Figure 2 - Microvascular dysfunction, referring to impaired function within the small blood vessels, affects multiple vital organs including the heart, brain, retina, lung, and kidney. Small vessel disease shares similar underlying mechanisms and can occur concomitantly. (*Legend*: ANOCA: angina with no obstructive coronary artery disease; HFpEF: heart failure with preserved ejection fraction; INOCA: ischemia with no obstructive coronary artery disease; MINOCA: myocardial infarction with no obstructive coronary arteries).

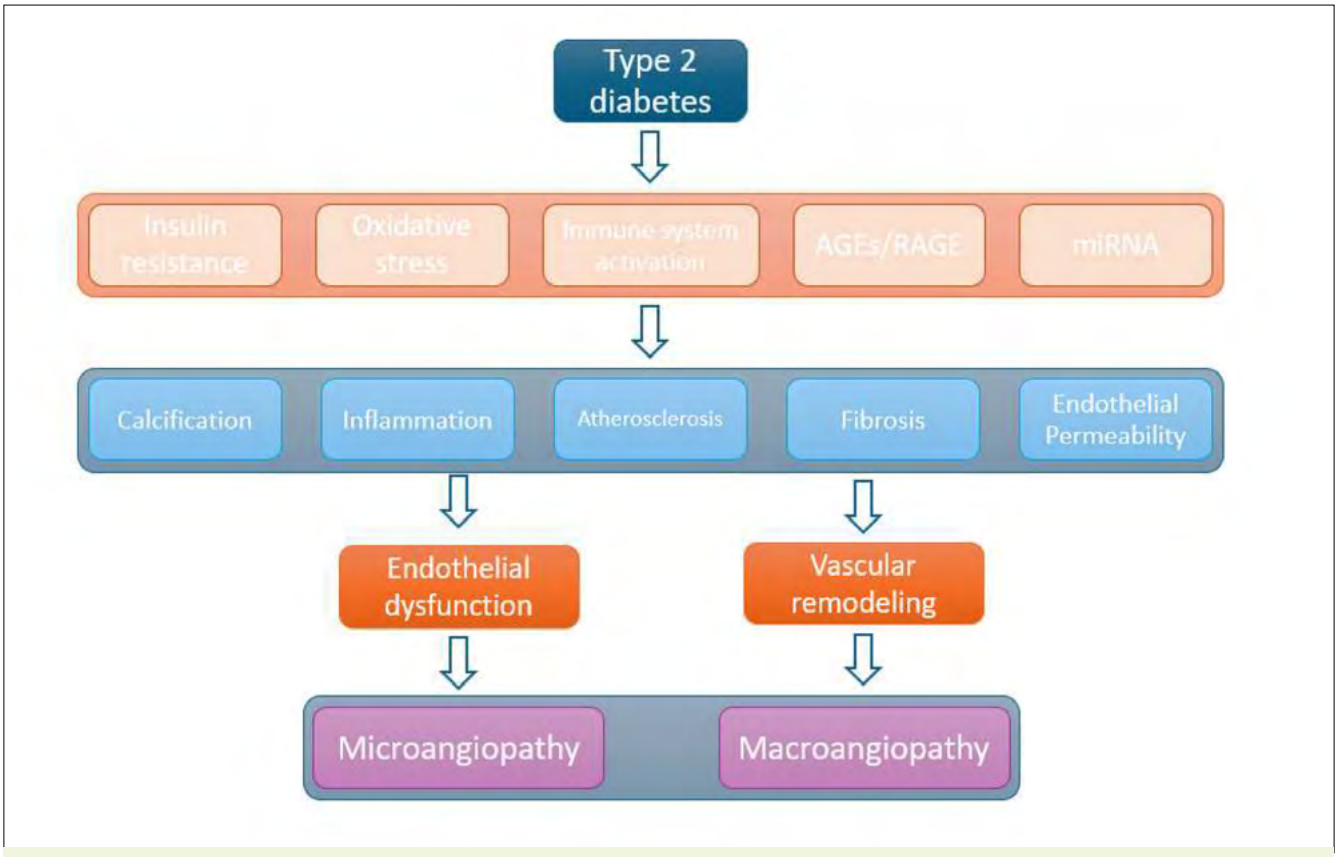

Figure 3 - The molecular mechanisms underlying vascular complications in diabetes.

a. Role of Endothelial Cells

Endothelial cells line the inner surface of blood vessels and play a crucial role in maintaining vascular homeostasis. In diabetes, endothelial cells become dysfunctional due to various pathological factors, including chronic hyperglycemia, insulin resistance, and dyslipidemia (Jansson, 2007; Bornfeldt, Tabas, 2011; Yaribeygi et al., 2019).

Endothelial dysfunction is characterized by reduced NO bioavailability, impaired production of vasodilators, increased oxidative stress, and concomitant impairment in endothelium-dependent vasodilation contributing to abnormal vascular tone (Tabit et al., 2010; Sena et al., 2008, 2011). In addition, endothelial dysfunction exhibits increased expression of adhesion molecules (e.g., von Willebrand factor, selectins), inflammation and platelet adhesion and aggregation, initiating the formation of blood clots (Avogaro et al., 2011). Endothelial dysfunction promotes increased vascular permeability, enhanced leukocyte adhesion, and abnormal angiogenic culminating in a pro-inflammatory, pro-oxidant, vasoconstrictor, prothrombotic environment (Sena et al., 2013).

b. Impaired Nitric Oxide Signaling

NO is a key signaling molecule produced by endothelial cells that regulates vascular tone, permeability, VSMC proliferation, platelet aggregation and inflammation. In diabetes, impaired NO bioavailability contributes to endothelial dysfunction and vascular complications (Sena et al., 2008; 2011). Reduced production of NO and increased degradation by ROS lead to vasoconstriction, endothelial activation, and pro-thrombotic responses (Sena et al., 2013). Additionally, dysregulated NO signaling contributes to impaired angiogenesis and microvascular rarefaction in diabetes (Fadini et al., 2019).

c. Increased Oxidative Stress

Chronic hyperglycemia and other metabolic abnormalities in diabetes lead to increased oxidative stress within the vascular wall. Excessive production of ROS overwhelms the antioxidant defense mechanisms of endothelial cells, leading to oxidative damage to lipids, proteins, and DNA and disruption of physiological processes (nucleic acid oxidation, lipid peroxidation; Giacco, Brown-

lee, 2010). Oxidative stress promotes endothelial dysfunction by impairing NO bioavailability, activating pro-inflammatory pathways, and promoting vascular remodeling. Additionally, ROS contribute to the formation of AGEs, further exacerbating endothelial dysfunction and vascular damage in diabetes (Sena et al., 2013). Strategies aimed at preserving endothelial function, restoring NO signaling, and reducing oxidative stress represent potential therapeutic approaches for preventing or ameliorating vascular complications associated with diabetes.

Inflammatory Pathways

The activation of inflammatory pathways in diabetes contributes to vascular dysfunction and the progression of vasculopathy through the upregulation of pro-inflammatory mediators, immune cell infiltration, and the promotion of endothelial dysfunction and atherosclerosis (Suárez-Rivero et al., 2021). Targeting inflammatory pathways represents a potential therapeutic approach for mitigating vascular complications in diabetes and preserving vascular health.

a. Activation of Inflammatory Cascades

Chronic hyperglycemia and insulin resistance in diabetes trigger the activation of inflammatory cascades within the vasculature. This involves the upregulation of various pro-inflammatory signaling pathways, including nuclear factor-kappa B (NF-κB), mitogen-activated protein kinases, and Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathways (Guo et al., 2024). Activation of these pathways leads to increased production of pro-inflammatory mediators, such as cytokines, chemokines, and adhesion molecules, promoting vascular inflammation and dysfunction (Matoba et al., 2019).

b. Role of Cytokines and Chemokines

Cytokines and chemokines play key roles in mediating vascular inflammation in diabetes. Pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6), are elevated in diabetes and contribute to endothelial dysfunction, VSMC proliferation, and leukocyte recruitment to the vessel wall (Sena et al., 2013; 2022). Chemokines, such as chemokine (C-C motif) ligand 2 (CCL2), promote the migration of immune cells, particularly monocytes and macrophages, to sites of vascular injury, further amplifying inflammation and tissue damage (Matoba et al., 2019).

c. Immune Cell Infiltration

Dysregulated inflammatory responses in diabetes lead to immune cell infiltration into the vessel wall. Monocytes, macrophages, and T lymphocytes are recruited to sites of vascular injury in response to chemokine signals. Once infiltrated, immune cells release pro-inflammatory cytokines, proteases, and ROS, exacerbating vascular inflammation and promoting the development of atherosclerotic plaques. Immune cell infiltration also contributes to endothelial dysfunction by disrupting NO signaling and promoting oxidative stress within the vessel wall (Girard et al., 2022).

Advanced Glycation End Products

AGEs are molecules formed by the non-enzymatic reaction between reducing sugars and amino groups of proteins, lipids, and nucleic acids (Thornalley, 2005; Twarda-Clapa et al., 2022). In diabetes, elevated blood glucose levels accelerate the formation and accumulation of AGEs through a process known as glycation. AGEs can accumulate in blood vessels and contribute to vascular dysfunction by promoting inflammation, oxidative stress, and cross-linking of proteins, which can impair vascular elasticity and function (Figure 4; Sena et al., 2011; Sena et al., 2012).

a. Formation and Accumulation

The formation of AGEs occurs through a series of complex chemical reactions, including glycation, oxidation, and rearrangement of sugar molecules (Thornalley, 2005). In diabetes, chronic hyperglycemia promotes the accelerated formation and accumulation of AGEs in various tissues, including the vascular wall. AGEs accumulate over time leading to increased tissue stiffness, impaired function, and structural alterations in blood vessels (Fishman et al., 2018).

b. Receptor-Mediated Signaling

AGEs exert their effects on vascular cells primarily through receptor-mediated signalling pathways, most notably the receptor for advanced glycation end products (RAGE). RAGE is expressed on endothelial cells, VSMC, immune cells, and other cell types within the vascular wall. Binding of AGEs to RAGE initiates intracellular signaling cascades, leading to the activation of pro-inflammatory pathways, oxidative stress, and endothelial dysfunction (Dong et al., 2022). Additionally, AGEs-RAGE

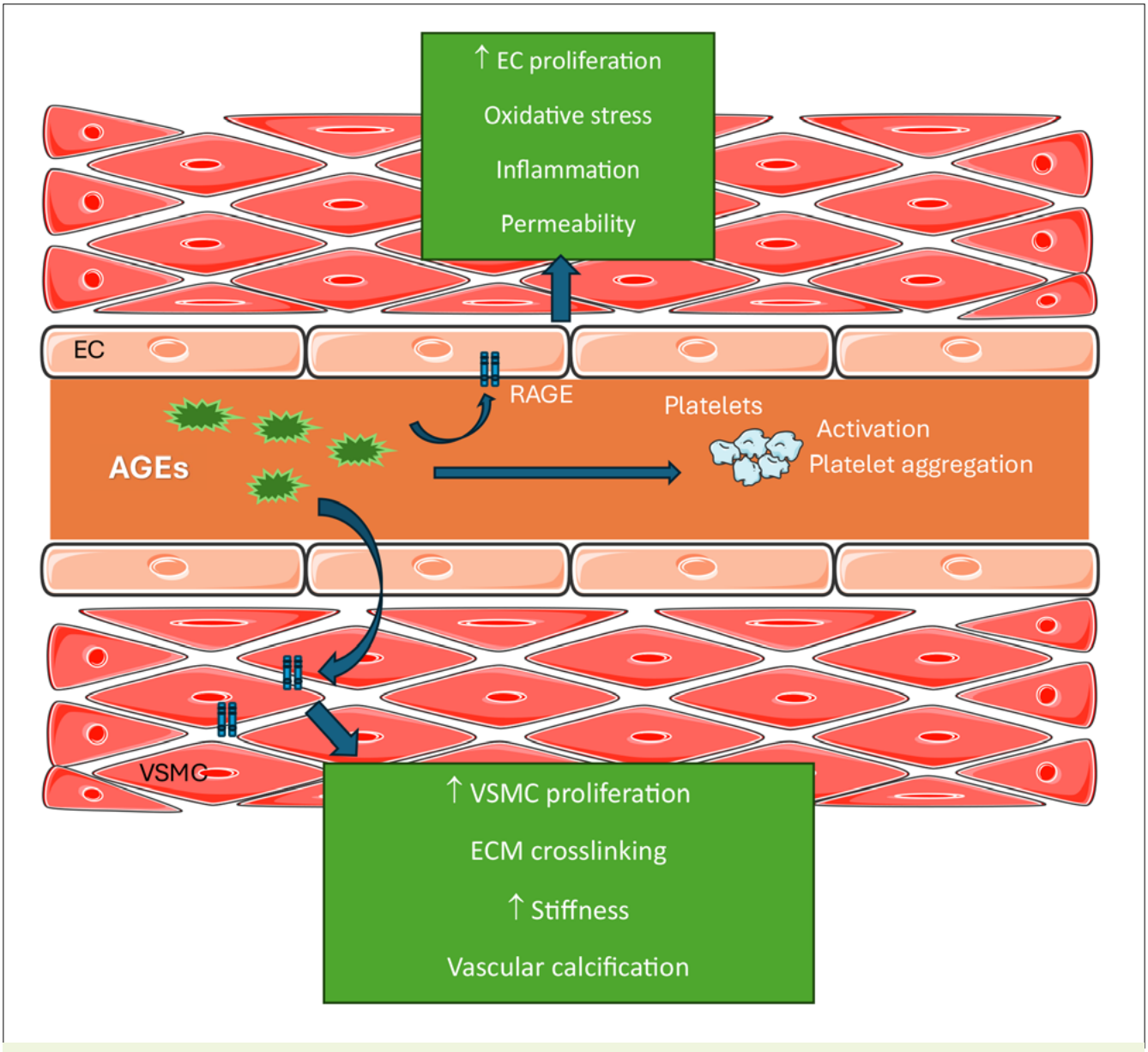

Figure 4 - Advanced Glycation End-products (AGEs) exert multifaceted effects within the vasculature, influencing various cellular processes through their binding to receptors such as RAGE and CD36 scavenger receptor. In the tunica intima, AGEs engage with endothelial cells' transmembrane receptor RAGE, setting off signaling cascades. This activation initiates pathways involving AP-1 and NF-κB, culminating in endothelial proliferation, inflammation, and heightened expression of pro-inflammatory cytokines. Additionally, AGEs prompt Reactive Oxygen Species (ROS) generation via NADPH oxidase, fostering NF-κB activation and inflammation. Direct effects include cytoskeletal reorganizations in endothelial cells, potentially increasing permeability. Moving to the tunica media, AGEs bind to RAGE in Vascular Smooth Muscle Cells (VSMCs), activating the ERK/MAPK pathway and subsequently inducing NF-κB and inflammatory cytokine production, along with metalloproteinase activation. This cascade promotes VSMC proliferation, inflammation, and extracellular matrix degradation. Overall, AGEs accumulation in the vascular lumen influences platelet activity and aggregation while exerting profound effects on endothelial cells and VSMCs, contributing to vascular dysfunction, inflammation, and calcification. These processes underscore the intricate interplay between AGEs and receptor-mediated signalling pathways in vascular pathophysiology.

interaction promotes the expression of adhesion molecules, cytokines, and growth factors, further exacerbating vascular inflammation and damage (Schmidt et al., 2015; Ruiz et al., 2020).

Intracellularly, circulating AGEs engage receptors for RAGE, expressed in monocytes, VSMC, and endothelial cells, inciting an inflammatory cascade via NF-κB activation, fostering growth factor expression, and adhesion molecule upregulation (Lin et al., 2022; Ruiz et al., 2020). Additionally, RAGE activation triggers oxidative stress

through nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, exacerbating vascular injury by binding to tissue-specific proteins and promoting local vascular damage (Wu et al., 2021). AGEs/RAGE interaction induces diverse effects on mononuclear macrophages, VSMC, and endothelial cells, including foam cell formation, autophagy induction, increased ROS and inducible nitric oxide synthase levels, and atherosclerotic plaque progression (Bao et al., 2020; Yamagishi, Matsui, 2018). Enhanced AGEs formation and hyperactivation of the hexosamine pathway contribute to the transcriptional regulation of angiopoietin-2, potentially explaining the persistence of vascular damage observed even after glycemic normalization (Hammes, 2018). Hyperglycemia-induced alterations in cellular epigenetics further underscore the long-term impacts beyond glycemic control, making epigenetics and AGEs critical intervention targets (Wu et al., 2023)

c. Impact on Vascular Function

AGEs contribute to vascular dysfunction through various mechanisms. Firstly, AGEs induced oxidative stress promotes the generation of ROS, leading to endothelial dysfunction, VSMC proliferation, and vascular inflammation. Secondly, AGEs cross-link with extracellular matrix proteins leading to increased vascular stiffness and reduced elasticity (Lin et al., 2023). This arterial stiffening contributes to hypertension, impaired vasodilation, and increased cardiovascular risk in individuals with diabetes. Lastly, AGEs-RAGE signaling promotes the expression of pro-inflammatory (see section b. Receptor-Mediated Signaling) and pro-thrombotic factors that contribute to the formation of atherosclerotic plaques (including the calcification), further exacerbating vascular complications (Figure 4; Taguchi, Fukami, 2023).

AGEs induce oxidative stress by ROS through various mechanisms, including activation of NADPH oxidase and mitochondrial dysfunction. ROS contribute to endothelial dysfunction, lipid peroxidation, and DNA damage, exacerbating vascular injury and promoting atherosclerosis (Yamagishi, Matsui, 2018).

AGEs form irreversible cross-links with proteins, altering their structure and function. AGEs bind crucial proteins within the extracellular matrix basement membrane, such as laminin, elastin, and collagen. Cross-linking of extracellular matrix proteins leads to increased stiffness and decreased elasticity of blood vessels, contributing to vascular remodeling and dysfunction. This process is particularly relevant in the context of diabetic complications (Yamagishi, Matsui, 2018; Taguchi, Fukami, 2023).

AGEs impair endothelial cell function by disrupting NO signaling, promoting vasoconstriction, and reducing vasodilation. AGEs-modified proteins also increase the expression of adhesion molecules and tissue factor, leading to enhanced thrombogenicity and atherogenicity (Yamagishi, Matsui, 2018; Taguchi, Fukami, 2023).

AGEs stimulate the production of profibrotic factors such as transforming growth factor beta (TGF-β), leading to the accumulation of extracellular matrix proteins and the development of vascular fibrosis. Vascular fibrosis contributes to arterial stiffening and impaired vasomotor function, further exacerbating vascular dysfunction. Moreover, AGEs influence coagulation, hemodynamics, vascular permeability, and tissue factor expression (Yamagishi, Matsui, 2018; Taguchi, Fukami, 2023).

Strategies aimed at reducing AGEs accumulation or blocking their detrimental effects represent potential therapeutic approaches for preventing or attenuating vascular complications associated with diabetes and aging.

Dysregulated Signaling Cascades

The following molecular pathways collectively contribute to the pathogenesis of vascular complications in diabetes, including atherosclerosis, microvascular dysfunction, peripheral arterial disease, and impaired wound healing (Creager et al., 2003a,b; Avogaro, Fadini,, 2019).

Hyperglycemia activates protein kinase C (PKC) isoforms in vascular cells, leading to increased production of pro-inflammatory cytokines, growth factors, and extracellular matrix proteins. PKC-mediated signaling also contributes to endothelial dysfunction, VSMC proliferation, and angiogenesis (Schäffler et al., 2000; Das Evcimen, King, 2007).

Increased glucose flux through the polyol pathway in diabetes leads to intracellular accumulation of sorbitol and fructose, causing cellular osmotic stress and oxidative damage. Polyol pathway activation contributes to endothelial dysfunction, neuropathy, and cataract formation (Giacco, Brownlee, 2010; Singh et al., 2021).

Elevated glucose flux through the hexosamine pathway results in the formation of AGEs and activation of PKC and NF-κB signaling pathways, contributing to vascular inflammation, oxidative stress, and endothelial dysfunction (Giacco, Brownlee, 2010; Gonzalez et al., 2023).

Targeting these pathways through lifestyle modifications, pharmacological interventions, and glycemic control strategies holds promise for preventing and managing diabetic vascular complications.

Dysregulated Angiogenesis

Dysregulated angiogenesis in diabetes contributes to vascular complications by impairing tissue perfusion, exacerbating ischemia, and promoting tissue damage (Kolluru et al., 2012). Understanding the molecular mechanisms underlying dysregulated angiogenesis in diabetes may offer insights into potential therapeutic strategies for preventing or ameliorating microvascular complications associated with the disease (Fadini et al., 2019).

a. Altered Growth Factor Signaling

Angiogenesis, the process of new blood vessel formation from pre-existing vessels, is tightly regulated by various growth factors, including vascular endothelial growth factor (VEGF), fibroblast growth factor, and angiopoietin. In diabetes, dysregulated signalling of these growth factors disrupts the balance between angiogenic and anti-angiogenic factors, leading to impaired angiogenesis. For example, chronic hyperglycemia in diabetes suppresses VEGF signaling, which is essential for endothelial cell proliferation, migration, and tube formation during angiogenesis. Additionally, increased levels of anti-angiogenic factors, such as thrombospondin-1 and endostatin, further inhibit angiogenesis in diabetes (Akbarian et al., 2022).

b. Impaired Vascular Remodeling

Angiogenesis plays a crucial role in vascular remodeling, the process by which blood vessels adapt to changes in blood flow, oxygen demand, and tissue metabolism. In diabetes, impaired angiogenesis hampers vascular remodeling, leading to inadequate tissue perfusion and ischemia (Eelen et al., 2020). This is particularly evident in conditions such as diabetic retinopathy and peripheral arterial disease, where impaired angiogenesis contributes to retinal ischemia, impaired wound healing, and tissue necrosis (Wu et al., 2022).

c. Capillary Rarefaction

Capillary rarefaction, the reduction in capillary density within tissues, is a hallmark of microvascular complications in diabetes. Dysregulated angiogenesis and impaired vascular remodeling contribute to capillary rarefaction by disrupting the balance between vessel growth and regression. Reduced capillary density exacerbates tissue hypoxia, oxidative stress, and inflammation, further promoting vascular dysfunction and tissue damage (Paavonsalo et al., 2020).

Mitochondrial Dysfunction

Mitochondrial dysfunction is increasingly recognized as a key contributor to vascular pathology in various diseases, including diabetes. Mitochondrial dysfunction plays a central role in the pathogenesis of vascular diseases by promoting oxidative stress, altering energy metabolism, and disrupting cellular homeostasis within the vascular wall (Tang et al., 2014; Qu et al., 2022).

a. Oxidative Stress and Mitochondrial Damage

Mitochondria are major sources of ROS production within cells. When mitochondrial function is impaired, there is an imbalance between ROS production and antioxidant defenses, leading to oxidative stress. ROS can damage mitochondrial DNA, proteins, and lipids, further impairing mitochondrial function in a vicious cycle (Coughlan et al., 2009; Gu et al., 2022). In the vasculature, oxidative stress resulting from mitochondrial dysfunction contributes to endothelial dysfunction, VSMC proliferation, and vascular inflammation, ultimately promoting atherosclerosis and other vascular complications (Dromparis, Michelakis, 2013; Qu et al., 2022).
Mitochondrial dysfunction arises from an imbalance in energy metabolic pathways, often resulting in compromised mitochondrial function characterized by increased mitochondrial autophagy and production of ROS (Tang et al., 2014). Mitochondrial function is crucial for maintaining cellular energy balance, and disruptions in glycolytic pathways, fatty acid oxidation, and certain amino acid metabolism under high glucose conditions can impact mitochondrial oxidative phosphorylation processes (Chen et al., 2023). Hyperglycemia leads to the production of AGEs and an increase in cytoplasmic ROS through the AGEs receptor (RAGE) pathway, promoting mitochondrial superoxide production and the onset of diabetic microangiopathy (Coughlan et al., 2009; Gu et al., 2022). The majority of ROS originate from mitochondrial complexes I and III, while the NADPH oxidases (NOX) family also contributes to mitochondrial ROS production, particularly NOX4, which is upregulated under various cellular stressors. Introducing novel mitochondria-targeted drugs has shown promise in improving the mitochondrial ROS/NLRP3 inflammasome axis and mitigating renal tubular injury in diabetic kidney disease (Matoba et al., 2019), with similar benefits observed in the myocardium, mitigating diabetic myocardial ische-

mia-reperfusion injury. The intramitochondrial protein p66Shc can further exacerbate mitochondrial ROS production by interfering with Ras activation or binding to cytochrome c (Di Lisa et al., 2017).

b. Altered Energy Metabolism

Mitochondria are crucial for cellular energy production through oxidative phosphorylation. In conditions of mitochondrial dysfunction, ATP synthesis is impaired, leading to altered energy metabolism within vascular cells. This metabolic dysregulation affects various cellular processes essential for vascular health, including vasodilation, vascular remodeling, and endothelial barrier function (Chen et al., 2023). Dysfunctional energy metabolism also leads to the accumulation of metabolic intermediates, such as lactate and succinate, which can further exacerbate vascular dysfunction and inflammation (Tang et al., 2014).

Mitochondrial energy metabolism varies among different organs, with the myocardium exhibiting abundant mitochondrial content. Alterations in mitochondrial function occur earlier in the myocardium of diabetic mice compared to the kidney, brain, and liver, indicating the importance of further mechanistic exploration in tissues with high mitochondrial content (Bugger et al., 2009).

Mitochondria also play a role in calcium ion storage and collaborate with the endoplasmic reticulum and extracellular matrix to regulate cellular calcium ion concentration dynamics, influencing cell cycle regulation and apoptosis (Bravo-Sagua et al., 2017).

High glucose levels can impact myocardial contractile function by upregulating sarcolipin, which promotes calcium sparks (Liu et al., 2020). Therapeutically, drugs like metformin inhibit mitochondrial respiratory chain complex-1 and regulate cellular energy metabolism (Wheaton et al., 2014). Metformin and glucagon-like peptide-1 (GLP-1) agonists additionally influence the GLP-1 pathway, bile acid pathway, and gut microbiota composition, indirectly impacting mitochondrial function (Akude et al., 2011; Foretz et al., 2019).

c. Implications for Vascular Health

Mitochondrial dysfunction has profound implications for vascular health and function.

Endothelial cells are particularly sensitive to mitochondrial dysfunction due to their high energy demand. Impaired mitochondrial function in endothelial cells leads to reduced NO bioavailability, increased oxidative stress, and inflammation, all of which contribute to endothelial dysfunction and vascular pathology (Sena et al., 2013; Chen et al., 2023). In VSMC, dysfunctional mitochondria promote excessive proliferation and migration, leading to vascular remodeling and arterial stiffness. Additionally, mitochondrial dysfunction in perivascular adipose tissue contributes to inflammation and oxidative stress, further exacerbating vascular dysfunction (Man et al., 2023).

Targeting mitochondrial dysfunction represents a promising therapeutic strategy for preventing or treating vascular complications associated with various diseases, including diabetes, cardiovascular disease, and aging.

Microvascular Complications

Microvascular complications primarily affect small blood vessels, including those in the eyes (retinopathy), kidneys (nephropathy), and nerves (neuropathy). Chronic hyperglycemia leads to damage of the delicate capillaries, impairing blood flow and nutrient delivery to affected tissues. In the eyes, this can result in diabetic retinopathy, a leading cause of blindness in adults. In the kidneys, diabetic nephropathy can progress to kidney failure (Giacco, Brownlee, 2010). Neuropathy can lead to numbness, tingling, and eventually, loss of sensation in the extremities. Overall, microvascular complications of diabetes can significantly impact quality of life and require comprehensive management approaches, including glycemic control, blood pressure management, regular monitoring, and lifestyle modifications (Giacco, Brownlee, 2010; Avogaro, Fadini, 2019). Early detection and intervention are crucial for preventing or delaying the progression of these complications and reducing the risk of long-term disability and mortality associated with diabetes (Gutierrez et al., 2019).

There is substantial evidence supporting the concept of microvascular dysfunction as a systemic and multi-organ pathological process. Various potential mechanisms have been suggested to explain these connections: in the heart and brain, microvascular dysfunction is linked to increased levels of homocysteine, serotonin, asymmetric dimethylarginine, and uric acid in the bloodstream, all of which disrupt the NO pathway (Gutierrez et al., 2019). This disruption in the NO pathway may also contribute to decreased bioavailable NO in chronic kidney disease, potentially raising the risk of cardiovascular events and worsening renal function. Further support for systemic endothelial dysfunction comes from studies like the Coronary Microvascular Angina study, where arterioles isolated from biopsies of patients with microvascular angina or variant angina showed reduced maximum relaxation with acetylcholine and increased

sensitivity to vasoconstricting agents (Ford et al., 2018). Moreover, conditions like systemic sclerosis and systemic lupus erythematosus demonstrate multi-organ involvement, with abnormalities observed in the skin, lungs, kidneys, heart, and gastrointestinal tract (Saygin et al., 2019). From a diagnostic standpoint, researchers have identified circulating biomarkers that are commonly associated with microvascular dysfunction in the heart, brain, and kidney (Figure 1), indicating involvement of various mechanistic pathways such as inflammation, coagulation/thrombosis, and endothelial dysfunction (Nowroozpoor et al., 2021).

a. Retinopathy

Diabetic retinopathy (DR) is a common complication of diabetes and a leading cause of blindness in adults (Das et al., 2021; Cheung et al., 2010). Chronic hyperglycemia damages the small blood vessels in the retina. The pathological cascade of DR commences with the loss of retinal neurons, followed by a series of events including early disruption of neurovascular coupling, retinal neurodegeneration, gliosis, and eventually culminating in retinal vasculopathy. Microvascular changes within the retina in DR are characterized by the loss of retinal capillary epithelial cells, reduced capillary elasticity, increased vascular permeability, exudation, local inflammation, and growth factors that promote neovascularization (Wang, 2018; Khansari et al., 2020). There are two main types of diabetic retinopathy: non-proliferative and proliferative. Non-proliferative retinopathy is characterized by microaneurysms, retinal hemorrhages, and hard exudates.

Proliferative retinopathy occurs when new, fragile blood vessels grow on the retina's surface, which can lead to retinal detachment and severe vision loss if left untreated (uch, Chew, 2022; Lechner et al., 2017). Regular eye exams and tight glycemic control are essential for preventing and managing diabetic retinopathy.

Delayed diagnosis and treatment remain primary contributors to visual impairment in diabetic patients, underscoring the importance of early detection and lesion prevention in DR. Biomarker-based investigations and artificial intelligence applications are anticipated to play increasingly significant roles in risk assessment, early diagnosis, and treatment of DR. Notably, elevated homocysteine levels in the serum of diabetic patients could serve as a screening and diagnostic indicator for DR, with potential interventions aimed at increasing homocysteine clearance (Elsherbiny et al., 2020). Additionally, factors such as VEGF and retinol-binding protein 3 hold promise as biomarkers and therapeutic targets for DR (Fickweiler et al., 2022). MiRNAs have also emerged as promising candidates, with certain miRNAs showing potential as biomarkers for DR severity (Helal et al., 2021; Hwang et al., 2022). Artificial intelligence, particularly in ophthalmology, offers a novel approach by integrating imaging databases with deep learning technology to aid in automated diagnosis and analysis of characteristic ocular structures in DR (Liu et al., 2022).

Understanding the underlying mechanisms of DR is imperative for its prevention and treatment. Hyperglycemia triggers inflammatory responses, oxidative stress, increased glycosylation product levels, and elevated VEGF levels, leading to alterations in retinal hemodynamics and increased retinal permeability, thereby contributing to the pathogenesis of DR. Furthermore, factors such as serine racemase overexpression, leukocyte adhesion, and aggregation, along with the release of inflammatory cytokines, exacerbate retinal damage and neovascularization in DR (Sergeys et al., 2019; Binet et al., 2020). Oxidative stress and chronic hyperglycemia further compound tissue damage, with various pathways including PKC activation, polyol pathway activation, and AGEs formation contributing to vascular complications and DR progression (Giacco, Brownlee, 2010; Kang et al., 2020).

b. Nephropathy

Diabetic nephropathy, also known as diabetic kidney disease, is a progressive condition characterized by damage to the kidneys' small blood vessels (Wimmer, et al., 2019). The kidneys' primary function is to filter waste products from the blood and regulate fluid balance. In diabetes, prolonged exposure to high blood glucose levels can damage the glomeruli, the tiny filtering units within the kidneys, leading to proteinuria, reduced kidney function, and ultimately, end-stage renal disease. Management strategies for diabetic nephropathy include tight glycemic control, blood pressure management with medications such as angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), and lifestyle modifications (Vallon, Komers, 2011; Goldman et al., 2020).

Diabetes is a leading cause of end-stage renal disease due to diabetic nephropathy. Hyperglycemia-induced activation of various pathways including PKC, polyol pathway, and the formation of AGEs contribute to renal damage. Additionally, dysregulation of the RAAS plays a critical role in the development and progression of diabetic nephropathy (Goldman et al., 2020; Wu et al., 2023).

c. Neuropathy

Diabetic neuropathy refers to nerve damage caused by diabetes, affecting various nerves throughout the body. Peripheral neuropathy is the most common form of diabetic neuropathy, characterized by tingling, numbness, burning sensations, or pain in the hands, feet, arms, or legs. Autonomic neuropathy affects the nerves that control involuntary bodily functions such as digestion, heart rate, and blood pressure, leading to symptoms such as gastroparesis (delayed stomach emptying), orthostatic hypotension, and sexual dysfunction (Lamotte, Sandroni, 2022). Proximal neuropathy affects nerves in the thighs, hips, or buttocks, causing weakness and pain. Tight glycemic control, pain management, and lifestyle modifications are essential for managing diabetic neuropathy and preventing further nerve damage (Pasnoor et al., 2013). Diabetes-induced microvascular damage and nerve ischemia contribute to the development of diabetic neuropathy. Several mechanisms including mitochondrial dysfunction, inflammation, and oxidative stress play roles in the pathogenesis of diabetic neuropathy (Zhu et al., 2024). The pathological mechanisms are the focus of current medications like PKC inhibitors and Aldose reductase inhibitors, which have a limited ability to slow the progression of neuropathy and are frequently linked to serious side effects. Effective and secure clinical treatment techniques still need to be explored to address this unmet medical need.

Perivascular Adipose Tissue

Perivascular adipose tissue (PVAT) contributes to vascular dysfunction in diabetes through the secretion of pro-inflammatory cytokines, oxidative stress, dysregulation of adipokines, insulin resistance, and pathological remodeling (Azul et al., 2020; Leandro et al., 2021).

PVAT, which surrounds the majority of blood vessels with the exception of the cerebral and pulmonary vasculature, has long been thought to serve primarily as a connective tissue to support vascular structure. Nowadays, PVAT is understood to be a physiologically autonomous endocrine tissue that preserves vascular homeostasis (Queiroz, Sena, 2020). PVAT is an active endocrine and paracrine organ that secretes various bioactive molecules, including adipokines, cytokines, and chemokines. In diabetes, dysregulated adipose tissue function leads to an imbalance in the secretion of these molecules, resulting in a pro-inflammatory state within the perivascular environment. Increased production of pro-inflammatory cytokines such as TNF-α, IL-6, and CCL2 from PVAT contributes to local inflammation and vascular dysfunction (Azul et al., 2020; Queiroz, Sena, 2020).

Perivascular adipose tissue dysfunction in diabetes is associated with increased oxidative stress. ROS generated by dysfunctional PVAT contribute to endothelial dysfunction, vascular inflammation, and oxidative modification of lipids and proteins within the blood vessel walls, exacerbating vascular dysfunction (Azul et al., 2020; Queiroz, Sena, 2020).

Dysfunction of PVAT in diabetes is associated with insulin resistance, a condition characterized by impaired responsiveness of tissues to insulin. Insulin resistance in PVAT leads to dysregulation of glucose and lipid metabolism, exacerbating local inflammation and oxidative stress, which contribute to vascular dysfunction (Man et al., 2023).

In diabetes, PVAT may undergo pathological changes, including fibrosis. Perivascular fibrosis can lead to stiffening of the perivascular environment, impairing the normal function of blood vessels and exacerbating vascular dysfunction (Azul et al., 2020; Man et al., 2023).

Targeting perivascular inflammation and dysfunction may represent a promising approach for the prevention and treatment of diabetes-related vascular complications.

Small Non-coding RNA molecules

Small non-coding RNA molecules, particularly miRNAs, play critical roles in the regulation of gene expression and have been implicated in various aspects of diabetes associated vasculopathy particularly in endothelial dysfunction, inflammation, and angiogenesis processes (Vasu et al., 2019).

MiRNAs play a crucial role in regulating endothelial cell function. Dysregulation of miRNAs in diabetes can contribute to endothelial dysfunction, characterized by impaired vasodilation, increased permeability, and enhanced leukocyte adhesion (Barutta et al., 2018). For example, miR-126 is one of the most studied miRNAs involved in endothelial function. It promotes endothelial cell survival, proliferation, and angiogenesis by targeting negative regulators of angiogenic signaling pathways. Reduced levels of miR-126 have been observed in diabetes, contributing to endothelial dysfunction and impaired angiogenesis (Rawal et al., 2017).

In addition, miRNAs are key regulators of inflammatory pathways involved in diabetes associated vasculopathy. Dysregulated miRNA expression can lead to aberrant activation of inflammatory signaling cascades, contributing to vascular inflammation and damage. For ins-

tance, miR-146a is known to suppress pro-inflammatory signaling pathways by targeting key mediators such as interleukin-1 receptor-associated kinase 1 and tumor necrosis factor receptor-associated factor 6. Reduced expression of miR-146a in diabetes results in enhanced inflammatory responses and endothelial dysfunction (Cheng et al., 2013).

MiRNAs play a crucial role in regulating angiogenesis. Dysregulated miRNA expression in diabetes can impair angiogenic responses, leading to inadequate tissue perfusion and impaired wound healing. MiRNAs such as miR-132, miR-27a, and miR-130a have been implicated in angiogenesis by targeting genes involved in endothelial cell proliferation, migration, and tube formation (Sun et al., 2018). Dysregulation of these miRNAs in diabetes contributes to impaired angiogenesis and microvascular complications.

MiRNAs can be packaged into extracellular vesicles (EV) such as exosomes and released into the circulation. EV--mediated transfer of miRNAs between cells facilitates intercellular communication and modulates vascular function in diabetes. EV-associated miRNAs derived from endothelial cells, immune cells, and perivascular tissues can influence gene expression and signaling pathways in recipient cells, contributing to vascular dysfunction and diabetic complications (Prattichizzo et al., 2021). Understanding the role of miRNAs in diabetes-associated vasculopathy provides insights into the molecular mechanisms underlying vascular dysfunction and identifies potential therapeutic targets for intervention. Modulating miRNA expression or activity holds promise for developing novel treatments aimed at preserving vascular health and preventing diabetic vascular complications (Vasu et al., 2019).

> THERAPEUTIC IMPLICATIONS

Addressing vasculopathy in diabetes requires a multifaceted approach that targets several pathways implicated in vascular dysfunction.

a. Targeting Molecular Pathways

Therapeutic strategies aimed at targeting specific molecular pathways involved in vascular dysfunction are being explored. For example, inhibitors of AGEs formation or receptor-mediated signaling pathways, such as RAGE inhibitors, may help mitigate AGE-induced vascular damage (Ruiz et al., 2020). Additionally, modulating inflammatory pathways, oxidative stress, and dysregulated angiogenesis represent promising therapeutic avenues for preventing or attenuating vascular complications in diabetes.

b. Pharmacological Interventions

Pharmacological interventions play a crucial role in managing vasculopathy in diabetes. Medications targeting cardiovascular risk factors, such as hypertension, dyslipidemia, and hyperglycemia, are essential for preventing or delaying the progression of vascular complications. ACE inhibitors, ARBs, statins, and anti-diabetic medications such as metformin, GLP-1 receptor agonists, and sodium-glucose co-transporter 2 (SGLT2) inhibitors are commonly used to improve vascular health and reduce cardiovascular risk in individuals with diabetes (Ndumele et al., 2023).

c. Lifestyle Modifications

Lifestyle modifications, including regular physical activity, healthy diet, weight management, smoking cessation, and stress reduction, are integral components of managing vasculopathy in diabetes. Physical activity promotes vascular health by improving endothelial function, reducing inflammation, and enhancing insulin sensitivity. A healthy diet rich in fruits, vegetables, whole grains, and lean proteins helps maintain optimal blood glucose levels, lipid profiles, and blood pressure, thereby reducing the risk of vascular complications (Lichtenstein et al., 2021; Diab et al., 2023).

> FUTURE DIRECTIONS AND RESEARCH CHALLENGES

One of the future directions in managing vasculopathy in diabetes involves the development of personalized therapeutic approaches tailored to individual patients' genetic, metabolic, and vascular profiles. Precision medicine approaches may help identify patients at high risk of vascular complications and optimize treatment strategies based on their specific needs and responses to therapy. Emphasizing prevention strategies, including early detection, intensive glycemic control, and aggressive management of cardiovascular risk factors, is paramount for reducing the burden of vascular complications in diabetes. Public health initiatives aimed at promoting healthy lifestyles and raising awareness about the importance of vascular health are essential for preventing diabetes-related vasculopathy and improving long-term outcomes for individuals with diabetes.

In addition, continued research is needed to identify novel therapeutic targets and biomarkers associated with

vascular dysfunction in diabetes. Exploring emerging molecular pathways, such as epigenetic modifications, non-coding RNAs, and mitochondrial dysfunction, may uncover new targets for therapeutic intervention.
Bridging the gap between basic science research and clinical practice is essential for translating promising preclinical findings into effective clinical therapies. Translational research efforts aimed at validating novel therapeutic targets, optimizing drug delivery systems, and conducting clinical trials are critical for advancing the field of diabetes vascular complications.

> CONCLUSION

In summary, addressing vasculopathy in diabetes requires a comprehensive approach that targets molecular pathways, utilizes pharmacological interventions, implements lifestyle modifications, and focuses on personalized medicine and preventive strategies.
Continued research efforts and collaboration across disciplines are essential for advancing our understanding of vascular dysfunction in diabetes and developing effective therapeutic interventions to improve outcomes for individuals with diabetes. <

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