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The status of studies on the mechanism of microcirculatory dysfunction in the process of diabetic kidney injury

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Abstract
Diabetic nephropathy (DN) is one of the most common and serious microvascular complications of diabetes mellitus (DM) and is the main cause of end-stage renal disease. Endothelial dysfunction caused by persistent hyperglycemia occurs at the initial stage of vascular disease. Moreover, persistent hyperglycemia is also a critical factor causing renal microcirculatory dysfunction. In recent years, many studies have confirmed that chronic hypoxia caused by microcirculatory dysfunction is one of the main mechanisms of kidney injury in patients with DM. Similarly, microcirculatory dysfunction damages renal tissue through interactions with other pathophysiological processes, thereby promoting the occurrence and development of DN. Thus, this article reviews the pathogenesis of renal microcirculatory dysfunction in DM and its interaction with stress, energy metabolism, and immunologic inflammation. Furthermore, a new idea was proposed to analyze the mechanism of kidney injury in DM from the perspective of microcirculatory dysfunction.

Keywords Diabetic nephropathy, Microcirculation, Endothelial dysfunction, Renal hypoxia, Inflammation

Introduction

Diabetes is a prevalent and challenging health problem of the 21st century, affecting an estimated 552 million people worldwide by 2030 [1]. As one of the most critical microvascular complications of diabetes, diabetic nephropathy (DN) is not only the primary cause of chronic kidney disease (CKD) but also the leading cause of end-stage renal disease (ESRD) worldwide. The main pathogenesis mechanisms of DN include inflammatory responses, oxidative stress (OS), hemodynamic changes, abnormal glucose metabolism, autophagy, and impaired immunity, ultimately leading to glomerular hypertrophy, glomerulosclerosis, tubulointerstitial inflammation, and fibrosis [2]. Many researchers believe that inflammation is central to the pathogenesis of DN [3–5]. However, some studies have shown that chronic hypoxia caused by renal microcirculatory dysfunction in diabetes mellitus (DM) is the main mechanisms leading to kidney injury [6, 7]. Notably, the onset of microcirculatory dysfunction is a characteristic feature in the early stages of DM [8]. Furthermore, microcirculatory dysfunction plays a major role in contributing to early kidney injury in DM and promoting the progression of DN [9] (as shown in Table 1). However, the mechanism of kidney injury caused by microcirculatory dysfunction is unclear. It may be related to energy metabolism, inflammatory responses, stress, apoptosis, epithelial–mesenchymal transition in renal

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Table 1 The characteristics of renal microcirculation in different stages of DN

Disease stages	Characteristics of renal microcirculation	Mechanism	Clinical manifestations
Early stages [6, 10–12]	Endothelial dysfunction. Peritubular capillary blood flow in the renal tubules begins to decrease.	Oxidative stress and inflammatory responses induced by persistent hyperglycemia. Intraglomerular hypertension.	Asymptomatic. Presence or absence of microalbuminuria.
Advanced stages [8, 13–15]	Progressive reduction in peritubular capillary blood flow. Significant increase in circulating endothelial cell numbers. Renal microvascular generation impairment.	Glomerulosclerosis. Renal interstitial fibrosis. Vascular homeostasis severely compromised.	Significant decline in renal function, presenting with symptoms of edema, anemia, and hypertension.

tubular cells, and excessive deposition of the extracellular matrix (ECM).

Methodology

This narrative review focuses on microcirculatory dysfunction in DN. We conducted a comprehensive literature search to identify relevant articles. The following databases were used: PubMed and the China National Knowledge Infrastructure. The search terms included "diabetes mellitus", "diabetic nephropathy", "microcirculation", "microcirculatory dysfunction" and "endothelial cell", combined with Boolean operators such as "AND" and "OR". Articles published between January 1984 and November 2024 were included to cover foundational research, clinical research, and recent advancements in the field.

In addition, manual retrieval of eligible literature involved three steps: (1) Preliminary Screening: Titles and abstracts of articles were reviewed to rapidly assess their relevance to the research topic. Articles that were clearly unrelated to the research theme were excluded. (2) In-Depth Screening: For articles identified as potentially relevant during the preliminary screening, the full texts were read to comprehensively evaluate their research content, methods, and results, determining whether they met the inclusion criteria. (3) Manual Screening: The references cited in articles meeting the inclusion criteria were manually reviewed to identify any potentially important literature that may have been overlooked.

Inclusion criteria were as follows: (1) The literature must be authentic, complete, free from citation errors, and accessible for retrieval and verification. (2) Experimental data must be comprehensive, analyses well-structured, and conclusions reliable. (3) The literature must focus on microcirculatory dysfunction in DN and methods for microcirculation assessment.

Exclusion criteria were as follows: (1) Articles with overly simplistic experimental designs or those insufficient to support their conclusions, such as studies limited to single-gene sequencing. (2) Studies with evident bias or conflicts of interest that compromise the objectivity of the research. (3) Literature for which the full text was unavailable or could not be downloaded.

Overview of microcirculatory dysfunction and detection techniques

The primary site of material exchange is the microcirculation. Notably, typical microcirculatory systems include arterioles, capillaries, and venules [16]. An abnormality in microcirculation structure and function causes the microcirculation to be unable to adapt to the metabolism level of tissues and organs and affects the material exchange of tissues and the function of organs, referred to as microcirculatory dysfunction [17]. Consequently, microcirculatory dysfunction may lead to changes in the physicochemical properties of the blood, narrowing of the lumen, slowing blood flow, or the formation of thrombi, leading to the failure of local tissues to perform routine functions due to ischemia and hypoxia, thus resulting in a series of clinical symptoms. DM, cardiocerebrovascular disease, tumors, hypertension, and other diseases are closely related to microcirculatory dysfunction [18–20]. Furthermore, the general characteristics of microcirculatory dysfunction include destruction of the microvascular structure, abnormal microvascular density, microvascular lumen stenosis, microvascular relaxation and contraction dysfunction, increased permeability of the vascular wall, abnormal blood perfusion, and changes in hemorheology and hemodynamics [21–23].

The current microcirculation detection technologies employed in medical research and clinical applications exhibit a trend toward diversification and precision, primarily aimed at assessing the hemodynamics, oxygen metabolism, and pathophysiological changes of microcirculation. Commonly utilized techniques include Nailfold Video-Capillaroscopy (NVC), Sidestream Dark Field Imaging (SDF), Contrast-enhanced Ultrasound (CEUS), Arterial Spin Labeling Magnetic Resonance Imaging (ASL-MRI), Laser Speckle Contrast Imaging (LSCI) and Two-photon Microscopy (TPM) (as shown in Table 2). These technologies hold significant value in the study of microcirculatory dysfunction associated with DN and the exploration of its pathological mechanisms. Additionally, they demonstrate broad potential applications in fields such as dermatology, cardiovascular diseases, and oncology. However, challenges remain in microvascular detection, such as the dynamic and heterogeneous nature of

Table 2 Main techniques for microcirculation detection

Modality	Principle	Detection indicators	Applicability	Advantages	Disadvantages	Application stage
NVC [24, 25]	Optical magnification	Microvascular density, diameter, shape, and branching patterns at the nail fold.	Diagnosis and assessment of systemic autoimmune diseases involving vascular abnormalities, such as systemic sclerosis.	Real-time, non-invasive, high-resolution, and low-cost.	The inability to quantify blood flow velocity. Image quality is highly dependent on the equipment and the technical expertise of the operator.	Applied to clinical diagnostics and research. Assessment of the health status of patients with DM.
SDF [22, 26]	By illuminating tissues with a specialized light source and leveraging the absorption of specific wavelengths of light by hemoglobin, blood vessels are visualized against a dark background.	Microvascular density, diameter and morphology. Red blood cell velocity. Microvascular flow index.	Suitable for assessing microcirculation in superficial tissues such as skin, oral mucosa, and conjunctiva.	Real-time, non-invasive, and high-resolution.	Prone to motion artifacts leading to image blurring. Challenging to observe deep tissues.	Primarily used in basic and clinical research. It has been applied in critical care monitoring but has not yet been widely adopted in clinical practice.
CEUS [27–31]	This technique quantifies tissue perfusion by leveraging microbubble contrast agents in conjunction with ultrasound imaging, enabling precise measurement of microcirculation.	Microvascular blood volume. Microvascular blood flow. Microvascular flow velocity. Time to peak. Peak intensity. Area under the curve.	Suitable for quantifying the microcirculatory status of deep organs, including skeletal muscle, heart, adipose tissue, kidneys, liver, and brain, it is particularly important in renal microcirculation studies.	Real-time, non-invasive, high-resolution, low-cost, and portable. The utilized ultrasound microbubbles (second-generation contrast agents) are non-nephrotoxic blood pool agents.	The results depend on the operator's technical expertise. Compared to MRI, CEUS has a relatively limited field of view, which prevents it from scanning an entire organ in one session.	Widely used in basic and clinical research. Due to the lack of standardized protocols for tissue perfusion quantification, it has not been widely adopted for microcirculation detection in clinical practice.
ASL-MRI [32–34]	Using water molecules in arterial blood as tracers, the magnetization state of the blood is altered through radiofrequency pulses. By comparing the signal differences between labeled and unlabeled blood in the perfusion area, microcirculation perfusion can be quantified.	Quantitative values of blood perfusion (e.g., ml/min/100 g).	This technique demonstrates excellent performance in assessing microcirculation perfusion in relatively stationary organs such as the brain and kidneys.	Non-invasive and high-resolution. ASL-MRI does not require exogenous contrast agents, making it suitable for patients of all ages and varying renal function statuses.	High-cost, complex operation, stringent requirements for the selection of scanning parameters, prolonged imaging time, and susceptibility to image noise and motion artifacts.	Primarily utilized in basic and clinical research.
LSCI [22, 35, 36]	The movement of red blood cells is tracked to assess blood flow within the vasculature, including the microvascular system.	Blood perfusion	Applicable for the evaluation of microvascular circulation in tissues and organs such as the retina, brain, skin, liver, and kidneys.	Real-time, non-invasive, cost-effective, and suitable for intraoperative use, capable of imaging multiple functional regions simultaneously while offering a wide field of view.	Relative measurements of blood flow, not absolute values; high sensitivity to motion artifacts.	Widely utilized in basic and clinical research. Not yet widely adopted in clinical practice but holds potential for clinical translation.

Table 2 (continued)

Modality	Principle	Detection indicators	Applicability	Advantages	Disadvantages	Application stage
TPM [37, 38]	This technique utilizes the principle of two-photon excitation, employing long-wavelength light sources to excite fluorescently labeled red blood cells or microvascular markers, enabling the tracking of blood flow direction and velocity as well as imaging the morphological structure of microvasculature.	Red blood cell velocity, capillary density, microvessel diameter.	Applicable for assessing the microcirculation in organs such as the brain, liver, pancreas, and kidneys.	Real-time, non-invasive, and high-resolution. Compared to conventional fluorescence microscopy, TPM offers superior background noise suppression, resulting in clearer imaging.	High-cost, complex operation, limited field of view and complicated data processing.	Primarily used in basic and clinical research.

microcirculation, which increases the complexity of measurements. Limitations in imaging deep tissues due to light scattering and signal attenuation, as well as the lack of standardization in techniques, further hinder the comparability of results. Consequently, most technologies for detecting microcirculation have not been widely applied in clinical diagnostics. In the future, advancements in technology optimization, the establishment of unified standards, and the integration of artificial intelligence-assisted analysis are expected to further enhance the precision of microcirculation detection, driving progress in disease diagnosis and treatment.

Pathophysiologic mechanisms of renal microcirculatory dysfunction in DM

DM causes microcirculatory dysfunction in many tissues and organs, including the heart [39], retina [40], skin [41], and kidneys. Currently, there is no unified definition of renal microcirculatory dysfunction in academia. The renal microcirculation system consists of two capillary beds: the peritubular capillary bed and the glomerular capillary bed. Notably, some scholars consider renal microcirculatory dysfunction to be an abnormality in the perfusion of renal capillary beds [42]. Moreover, other scholars have used the levels of β2-microglobulin, urinary microalbuminuria (mALB), serum Cystatin C, and uric acid as criteria for determining renal microcirculatory dysfunction [43]. However, the mechanism of renal microcirculatory dysfunction in DM has not been fully elucidated. Several mechanisms have been proposed, including the accumulation of advanced glycation end products (AGEs) [44, 45], the reduction of nitric oxide (NO) synthesis [46], activation of the hexosamine biosynthesis pathway (HBP), activation of the polyol pathway [47], abnormal activation of the renin–angiotensin–aldosterone system [48, 49], and protein kinase C (PKC) activation [47] (shown in Fig. 1).

Relationships between endothelial cell injury and microcirculatory dysfunction

Endothelial dysfunction is defined as the loss of endothelial vasodilatory, anticoagulant, and anti-inflammatory properties and the predominance of mechanisms that promote thrombosis, vasoconstriction, and inflammation in the arterial wall resulting from reduced NO availability [50]. Notably, endothelial dysfunction is the initial stage of vascular disease, precedes the occurrence of microvascular disease, and may cause microvascular disease [51]. Thus, endothelial dysfunction plays an essential role in DM-related vascular complications [50]. Persistent hyperglycemia in DM patients is the initial factor leading to microcirculatory dysfunction. Clinical studies have shown that endothelial dysfunction markers, including elevated serum von Willebrand factor (vWF) and increased capillary albumin leakage rate, can be observed prior to the onset of mALB in Type 1 DM. These markers worsen as mALB develops [52, 53]. Some patients with Type 2 DM may develop mALB in the absence of signs of endothelial dysfunction; however, in other patients, vWF levels can still predict the progression to mALB [54]. Therefore, the close association between endothelial dysfunction and mALB in DM may serve as the basis for the predictability of DN progression.

Increased production of advanced glycosylation end products

In persistent hyperglycemia, glucose can react with proteins in the body via nonenzymatic glycation, forming many AGEs [11]. Likewise, AGEs are observed in cases of diabetic glomerulopathy [55]. Importantly, AGEs cause biological changes in target cells and contribute to the development of diabetic complications by directly interacting with proteins or combining with receptors for advanced glycation end products (RAGE) [11, 56]. In a study in which AGEs increased endothelial cell permeability, the phosphorylation of VE-cadherin was found to be approximately 2-fold greater when the cells were exposed to 100 μg/mL AGEs for 1 h [57]. Simultaneously,

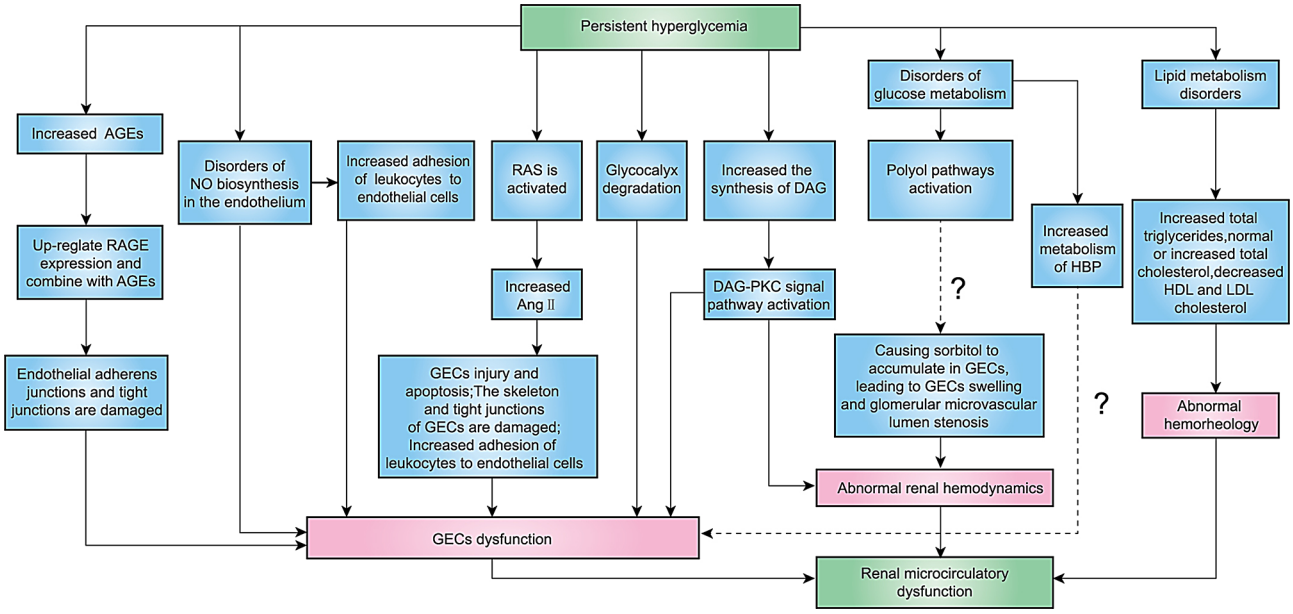

Fig. 1 Mechanism of renal microcirculatory dysfunction in Diabetes Mellitus

many studies have shown that the phosphorylation of endothelial adherens junction components promotes the weakening of intercellular connections and the opening of the endothelial barrier [58–60]. Additionally, increased AGEs can upregulate RAGE expression and combine with it, resulting in structural changes in VE-cadherin [61, 62] and destroying the continuous distribution of tight junctions between endothelial cells (claudin-5, occludin, ZO-1, etc.) [63], ultimately increasing the permeability of endothelial cells. Notably, renal tissue is rich in RAGE, and RAGE is also expressed in human glomerular endothelial cells (GECs) [64]. Thus, the kidney is susceptible to AGEs. Other studies have shown that the binding of AGEs and RAGE can trigger the release of proinflammatory cytokines and chemokines, activate the NF-κB signaling pathway, and cause OS [65]. The OS can subsequently damage the integrity of the endothelium by reducing the expression of tight junctions and activating matrix metalloproteinases [66].

While these studies underscore the role of AGEs in endothelial dysfunction, certain limitations warrant attention. For example, the commonly applied high-concentration AGEs exposure may not accurately reflect physiological conditions, thus potentially restricting real-world applicability. Additionally, variability in sample sizes and cell types compromises reproducibility across studies; For instance, in the study by Zhang et al. [57], all tests were conducted with a limited sample size of $n = 3$. Future research should incorporate more representative AGEs concentrations and a broader array of models to further validate these mechanisms.

Oxidative factors effect of decreased nitric oxide synthesis

NO is a critical endothelium-derived vasodilator, and its synthesis and bioavailability reduction can impair vascular endothelium diastolic function and increase endothelial cell permeability [66, 67]. In addition, NO can block the transcription of several adhesion molecule mRNAs, such as vascular cell adhesion molecule-1 and intercellular adhesion molecule-1 (ICAM-1), and inhibit the adhesion of leukocytes to endothelial cells, thus playing a crucial role in protecting endothelial cells from inflammatory injury [68, 69]. Reduced NO production is a manifestation of endothelial dysfunction and is an important determinant of various vascular pathologies [70].

Endothelial nitric oxide synthase (eNOS) is the key enzyme responsible for the generation of endothelial cell-derived NO [70]. Reduced eNOS activity or expression results in decreased NO production [51]. Importantly, eNOS is primarily located in endothelial cells. Activation of eNOS increases NO synthesis, contributing to vasodilation, enhancing local blood supply, reducing leukocyte adhesion, and preventing endothelial cell injury. Studies have shown that during the progression of DM, the insulin signaling pathway was inhibited, leading to reduced eNOS activity and NO bioavailability, thereby impairing endothelial vasodilatory function [71]. eNOS expression levels are upregulated in the glomeruli of rats during the early stages of DN, leading to increased NO production [72, 73]. A similar result was observed in endothelial cells cultured under high glucose conditions, where eNOS expression increased along with elevated NO production. However, high glucose also synchronously enhanced the generation of O_2- (a product of OS), which can inactivate NO and lead to endothelial dysfunction in vasodilation

[74]. Therefore, even in the early stages of DN, despite the increase in NO production, the presence of OS impairs NO bioavailability, which can still lead to endothelial dysfunction. In mice with late-stage DN, renal eNOS is not only downregulated in expression but also decreased in activity, leading to reduced NO production. This may be a critical factor in the pathological progression of late-stage DN [73]. This conclusion is supported by findings from a study on diabetic rats, where the levels of tetrahydrobiopterin (BH_4) in diabetic rats were significantly lower than those in non-diabetic rats (0.17 ± 0.01 vs. 1.42 ± 0.22) [75]. BH_4 is an essential cofactor for eNOS, and its deficiency can lead to eNOS "uncoupling", altering eNOS activity, reducing NO production, and causing endothelial dysfunction [75]. Based on cellular and animal experiments, Paolo Tessari further elucidated the mechanism of NO reduction in late-stage DN, pointing out that, in addition to BH_4 deficiency, eNOS "uncoupling" due to OS and inflammation, as well as increased levels of asymmetric dimethylarginine, are all contributing factors to the decrease in NO production [76].

Research on eNOS and NO in DN is largely based on cellular or animal models, whose applicability and limitations require careful consideration. For instance, analyzing NO production and BH_4 level changes in DN using diabetic rat models may limit the generalizability of the conclusions, as the genetic background and metabolic characteristics of rats differ from those of humans. Interestingly, another study demonstrated that high glucose concentrations had no significant effect on eNOS activity and expression in human umbilical vein endothelial cells (HUVECs), whereas AGEs significantly inhibited eNOS activity and expression in a concentration- and time-dependent manner [77]. This suggests that differences may exist between various cell types and experimental models. Future research should carefully select experimental conditions and further validate these findings before clinical application.

In summary, NO has a significant impact on microcirculation, and its role in the progression of DN exhibits stage-specific characteristics. Although current research supports the understanding of the role of NO in endothelial function in DN, there are differences in the experimental models used across studies. Future research should place greater emphasis on human studies to further elucidate the specific mechanisms of NO in the progression of DN.

DAG-PKC signaling pathway activation

PKC is an important molecule involved in cell signal transduction and plays a vital role in the vascular complications of DM [78]. Under diabetic conditions, the hyperglycemic environment increases the synthesis of diacylglycerol (DAG) through the glycolytic pathway, thereby activating PKC, particularly the PKC-β isoform, which includes PKC-β1 and PKC-β2 [79–81]. This activation can occur in intrinsic renal cells, particularly in GECs and mesangial cells (MCs) [78]. In the context of DM, in addition to the increase in DAG synthesis induced by hyperglycemia, AGEs, activation of the polyol pathway, and elevated OS levels further promote DAG production, thereby more effectively activating PKC [80]. The multi-factor-driven activation of the DAG-PKC signaling pathway induces pathological changes in the kidney, including increased endothelial cell permeability to albumin, mesangial expansion, enhanced synthesis of fibrotic molecules such as transforming growth factor-β (TGF-β), and alterations in renal hemodynamics [80].

Notably, PKC activation is involved in microvascular constriction in the kidney, affecting glomerular function and promoting the progression of DN [78]. The activation of PKC disrupts the balance between thromboxane A2 and prostacyclin, leading to vasoconstriction and thrombosis [82]. The activation of PKC also increases the production of endothelin-1 and enhances the effects of angiotensin II (Ang II) [82, 83]. Regarding eNOS, activation of PKC can phosphorylate eNOS, significantly inhibiting its activity and reducing NO production. This effect has been observed in bovine aortic endothelial cells and murine MCs [84, 85]. Similar studies have also shown that in the glomeruli of diabetic rats, the activation of PKC reduces NO and NO-dependent cyclic guanosine monophosphate production, leading to impaired vasodilation, increased vasoconstriction, and consequently exacerbating microvascular damage in the kidneys [86]. Moreover, specific PKC-β inhibitors can increase blood flow perfusion and maintain endothelium-dependent vasodilation under high-glucose conditions, thereby improving endothelial dysfunction [87].

Additionally, the activation of PKC induces the expression of vascular endothelial growth factor, a factor that enhances vascular permeability, thus exacerbating vascular damage [88]. A cell study also found that PKC is a key mediator of ICAM-1 expression and promotes monocyte chemotaxis under high-glucose conditions [89].

Based on the above studies, we propose that under diabetic conditions, activation of the DAG-PKC signaling pathway alters the synthesis and function of multiple vasoactive factors within the kidney, which may ultimately result in renal microcirculatory dysfunction.

Renin–angiotensin system disorder

High glucose causes an imbalance of the renin–angiotensin system (RAS) in the glomerulus, which results in a large amount of AngII (the central effector molecule in the RAS) [90]. Additionally, the efferent arteriole is more sensitive to Ang II than the afferent arteriole is, and Ang II has a more significant effect on the efferent arteriole.

As a result, AngII can increase renal blood flow resistance, resulting in glomerular hypertension, high permeability, and hyperfiltration, damaging the structure of the glomerular filtration barrier (GFB) [91, 92]. A study in animals has also shown that changes in the microcirculatory structure (expansion of afferent arterioles) cooccur with glomerular hyperfiltration in the early stages of DM, and subsequently, proteinuria appears [93]. These findings suggest that microcirculatory dysfunction may be the cause of glomerular hyperfiltration. Likewise, high glucose can activate the RAS of GECs and produce AngII. AngII can impair the function of endothelial cells by binding to its receptors, the angiotensin II type 1 receptor (AT1R) and the angiotensin II type 2 receptor, thus contributing to the progression of DN in rats [94]. Notably, the application of an angiotensin-converting enzyme inhibitor or Angiotensin II Receptor Blockers can reduce AngII-induced GECs injury and apoptosis [95, 96] and improve glomerular hemodynamics [93].

In addition, the RAS can affect the skeleton and tight junctions of GECs, significantly enhancing their permeability. The expression of RAGE in GECs increases in a concentration-dependent manner when GECs are stimulated with different concentrations of AGEs in vitro, thereby activating the RAS in GECs and leading to the destruction of tight junctions between cells [63]. AngII might contribute to tight junctions degradation by promoting the activation of matrix metalloproteinase-9 and nicotinamide adenine dinucleotide phosphate oxidase 4 (NOX4) [97]. Additionally, Ang II can depolymerize filamentous actin (the main component of the cytoskeleton, which plays a vital role in maintaining GECs' barrier function), leading to cell contraction and the formation of intercellular fissures [98]. As mentioned earlier, AngII and NO play essential roles in altering endothelial permeability, and AngII activates the production of NO in endothelial cells, resulting in eNOS uncoupling [99].

Endothelial glycocalyx degradation

GECs are the first-layer structure of the GFB. There are 200–400 nm thick negatively charged polysaccharide–protein complexes called the endothelial glycocalyx on the side of the cavity of GECs; these complexes cover the surface of GECs and have important barrier functions. The endothelial glycocalyx is composed of proteoglycans, glycolipids, and glycoproteins. Additionally, proteoglycans are composed of glycosaminoglycans and core proteins, and glycosaminoglycans include chondroitin sulfate, hyaluronic acid, heparin sulfate, and keratan sulfate [100]. Furthermore, the endothelial glycocalyx is an essential component of the GFB and plays a role in regulating glomerular permeability.

In physiological states, the endothelial glycocalyx allows only water and small solutes to filter into Bowman's capsule. However, high blood sugar results in a loss of the glycocalyx, which can lead to endothelial dysfunction and increased vascular permeability [101, 102]. The degradation of chondroitin sulfate and hyaluronic acid in the mouse kidney results in a negatively charged endothelial glycocalyx. It increases the glomerular filtration of albumin but does not change the clearance of neutral protein, which is close to the molecular weight of albumin. Michael Crompton et al. also demonstrated that DM can damage the endothelial glycocalyx in humans and rats, and protecting it can reduce glomerular permeability and improve albuminuria [103]. Meanwhile, cell experiments have also confirmed that the endothelial glycocalyx of human GECs acts as a permeability barrier for macromolecules [104]. Moreover, there is no significant change in podocytes (PCs) in many patients with early-stage proteinuria with DN. GECs remain key structures regulating glomerular microvascular permeability even with impaired PCs [105–107].

Relationships between metabolic disorders and microcirculatory dysfunction

Disorders of glucose metabolism

Aldose reductase (AR) is the rate-limiting enzyme of the polyol pathway [108]. Under physiological conditions, the affinity of AR for glucose is very low, and the polyol pathway is inhibited. Under the stimulation of continuous hyperglycemia, AR and the polyol pathway are activated, and AR transforms a large amount of glucose into sorbitol, which is slowly metabolized and makes it difficult for it to penetrate the cell membrane [109]. Importantly, sorbitol accumulation occurs in cells, resulting in a hyperosmolar state and cellular edema [110]. Sorbitol can also accumulate in the endothelial cells of diabetic retinal tissue and cause endothelial cells to swell [111]. Notably, some scholars have reported that high sugar contents significantly increase the amount of sorbitol in human GECs [112]. Therefore, the authors speculate that DM can cause sorbitol to accumulate in GECs, leading to GEC swelling and glomerular microvascular lumen stenosis.

After glucose enters the cell, most of it is metabolized through glycolysis, glycogen synthesis, and the pentose phosphate pathway. Only approximately 1–3% of glucose enters the HBP. When the metabolism of other sugars slightly changed, the HBP increased 3–5-fold. Glutamine: Fructose-6-phosphate aminotransferase (GFAT) is the key and rate-limiting enzyme of the HBP. Thus, interfering with the HBP may prevent or delay the development of dysfunction in resistant arteries in patients with DM. Therefore, blocking the HBP is considered a novel target for preventing vascular complications of DM [113]. In prolonged hyperglycemia, glucose is absorbed by glucose transporters, converted into glucosamine-6-phosphate,

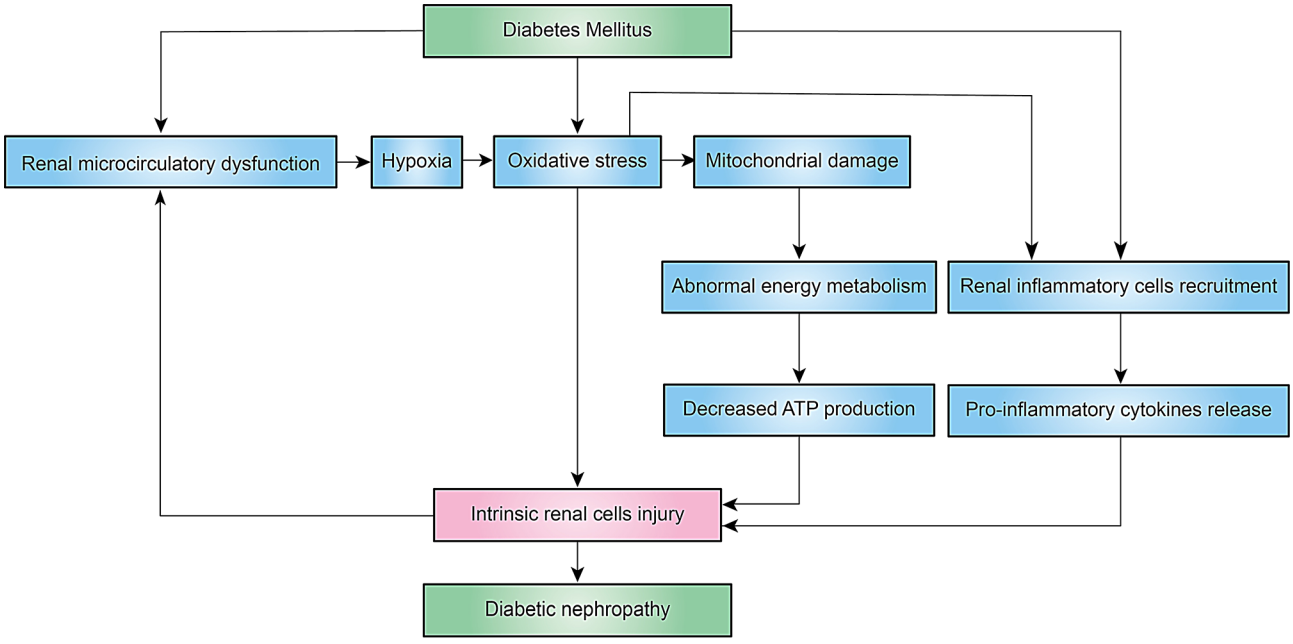

Fig. 2 Mechanism of diabetic nephropathy

and further metabolized into uridine diphosphate N-acetylglucosamine (UDP-GlcNAc). UDP-GlcNAc is the main substrate for the formation of O-linked beta-N-acetylglucosamine (O-GlcNAc) on serine and threonine residues of many proteins, including eNOS. The increase in GFAT activity and O-GlcNAc levels was also found to be related to insulin resistance and type II diabetes mellitus [114, 115]. The link between HBP and endothelial dysfunction is that O-GlcNAc glycosylation competes with protein kinase B (AKT) in the phosphorylation of eNOS, thereby reducing the production of NO [116, 117]. Furthermore, this study revealed that vitamin D may reduce DN by increasing blood glucose and insulin levels and modulating the HBP. It may also help prevent DN by reducing the production of GFATs in renal tissue [118].

Lipid metabolism disorders

DM is usually accompanied by lipid metabolic disorders, which are independent risk factors for the occurrence and development of DM and DN [119]. The main manifestations of lipid metabolic disorders in DN patients include increased triglycerides, normal or elevated total cholesterol, and decreased high-density lipoprotein cholesterol, along with increased low-density lipoprotein cholesterol. Increasing plasma lipids and lipoproteins can increase blood viscosity, the main factor affecting hemorheology. The deformability and aggregation of red blood cells are also related to the increase in lipids [120, 121]. In addition, hyperlipidemia can cause damage to vascular endothelial cells, platelet aggregation, decreased fibrinolytic enzyme activity, and the release of vasoconstrictive active substances in the kidney. Therefore, these factors can lead to changes in hemorheology and subsequently cause renal microcirculatory dysfunction [122].

Mechanism of microcirculatory dysfunction in diabetic renal injury

Renal tissue hypoxia may be a common mechanism for CKD (including DN). Notably, renal tissue hypoxia in DM patients precedes albuminuria, thereby being a reasonable cause for the onset and progression of DN [7, 123]. According to recent studies, one of the critical causes of renal damage is chronic hypoxia caused by renal microcirculation dysfunction in patients with DM [7, 124]. Through interactions involving stress, energy metabolism, immunologic inflammation, and other pathophysiological processes, microcirculatory dysfunction damages renal tissue cells and promotes the occurrence and development of DN (shown in Fig. 2).

Microcirculatory dysfunction and stress

Oxidative stress

Under various types of adverse stimuli, the body produces many reactive oxygen species (ROS) and reactive nitrogen species (RNS), the production of oxides exceeds the elimination of oxides, and the body's ability to defend against oxidation decreases, affecting the balance of oxidation and antioxidation systems and resulting in histiocytic damage and even cell death [125]. By attacking cytoplasmic membranes too often, free radicals cause lipid peroxidation and lead to various lipid peroxidation products, including malondialdehyde (MDA). The amount of MDA produced by rat renal microvascular

endothelial cells increased with increasing AGEs concentration in the culture medium [126]. Additionally, the accumulation of MDA can cause intramolecular or intermolecular protein/DNA crosslinking, leading to damage to the cellular structure and dysfunction [127]. Furthermore, the study revealed that MDA can reduce the survival rate of HUVECs under high glucose conditions and promote HUVEC apoptosis. Moreover, compared with the control, MDA increased the transcription level of the proapoptotic gene Bax by approximately 1.8-fold. However, the transcript level of Bcl-2 decreased [128]. Animal experiments demonstrated that diabetic mice (db/db mice and streptozotocin-induced diabetic mice) had significantly lower levels of antioxidant enzymes and higher levels of ROS in renal tissues compared to non-diabetic mice, along with marked impairment in renal function [129, 130]. Cell experiments demonstrated that high glucose conditions can lead to excessive ROS production in HUVECs, subsequently inducing pyroptosis [131]. The above studies indicate that hyperglycemia can induce OS in GECs, leading to cellular damage.

Hong et al. suggested that DM can lead to adaptive changes in microcirculation, such as vascular remodeling and alterations in angiogenesis, thereby affecting blood flow and oxygen delivery, which in turn exacerbates oxidative stress [132]. Zhao et al. successfully induced OS in endothelial cells by simulating the microenvironment of microcirculatory dysfunction under diabetic conditions in vitro, specifically under high glucose and hypoxic cell culture conditions [133]. These pieces of evidence suggest that DM-induced microcirculatory dysfunction can lead to or exacerbate OS.

DM-induced excessive mitochondrial ROS production plays a critical role in the pathogenesis of DN [134, 135]. Excessive ROS production gradually impairs mitochondrial function, leading to reduced efficiency of the electron transport chain, which in turn further increases ROS levels and decreases ATP production [136]. The double-membrane structure of mitochondria contains a high content of unsaturated fatty acids, primarily docosahexaenoic (22:6 n3) and arachidonic (C20:4 n6) acids, which are highly susceptible to lipid peroxidation and particularly vulnerable to attack by ROS [137, 138]. Excessive ROS can lead to lipid peroxidation of the membrane and trigger abnormal opening of the mitochondrial permeability transition pore, thereby increasing permeability and allowing proteins to enter the intermembrane space. These negatively charged proteins are released into the cytosol, resulting in the backflow of positive ions from the intermembrane space to the matrix. Subsequently, the ionic gradient across the mitochondrial inner membrane dissipates, mitochondrial membrane potential decreases, oxidative phosphorylation becomes uncoupled, and ATP synthesis is inhibited [138, 139]. Meanwhile, the higher concentration of positive ions in the mitochondrial matrix compared to the cytosol exacerbates mitochondrial swelling, potentially leading to rupture. In addition, DM-induced excessive ROS can also damage mitochondrial proteins and DNA, further leading to mitochondrial dysfunction and structural damage [140]. Generally, ROS and mitochondrial dysfunction interact with each other, creating a cause-and-effect relationship that forms a vicious cycle. Additionally, increased vasoconstriction results from excessive mitochondrial ROS synthesis, which decreases NO bioavailability in endothelial cells [141, 142]. Thus, mitochondrial ROS are closely related to vascular endothelial cell regulation.

One of the sources of ROS in the vascular system is the NOX family, which regulates renal microcirculation perfusion. Mitochondrial NOX4 is a major source of ROS in many cell types and kidney tissues of DM animals. NOX is involved in the increase in Ang II-induced ROS. Ang II and adenosine, which are upregulated in renal microvessels, bind to the adenosine A1 receptor and AT1R, respectively, to activate NOX and increase the generation of superoxide [143]. As mentioned above, hyperglycemia activates the RAS, which increases the expression of AngII, a factor involved in the development of microcirculation diseases. Therefore, our team believes that the microcirculatory dysfunction and OS in DM kidneys share the same triggering factor, such as the upregulation of Ang II.

Cytochrome b558, formed by the combination of NOX2 and P22phox, is the catalytic core of NOX [144]. In the Ang II-infused rat model, Ang II can cause OS by binding to AT1R, thus increasing the expression of p22phox and NOX1 mRNAs in the renal cortex. Liu Yuling suggested that the overexpression of P22phox in blood vessels is involved in vascular endothelium injury [145]. Notably, the reduction in OS levels caused by the application of NOX inhibitors attenuates Ang II-mediated vasoconstriction, suggesting that ROS play an essential role in Ang II-mediated vascular effects [143].

DM-induced OS and microcirculatory dysfunction play a critical role in the pathogenesis of DN. Excessive production of ROS, driven by mitochondrial dysfunction and NOX activation, leads to significant cellular damage, including endothelial cell injury, mitochondrial impairment, and disruption in vascular regulation, which forms a vicious cycle, exacerbating renal OS and further impairing renal microcirculation, ultimately contributing to the progression of DN.

Endoplasmic reticulum stress

Endoplasmic reticulum stress (ERS) refers to the disordered physiological function of the endoplasmic reticulum (ER) under the action of several stimulatory factors, which leads to the accumulation of unfolded or misfolded

proteins in the endoplasmic reticulum lumen. Furthermore, it leads to a pathological state of endoplasmic reticulum dysfunction. Numerous studies have demonstrated that ERS is a key pathophysiological process in DM-induced kidney damage and that ERS contributes to the harm caused to GECs, MCs, PCs and renal tubular epithelial cells in DN [146–149]. Importantly, the application of Src kinase inhibitors can increase OS and renal structure and function, decrease inflammation, and lower ERS signaling, all of which reduce kidney injury in DM rats [150].

DM and endothelial impairment are both intimately connected to ERS activation [151]. Cellular experiments have demonstrated that high glucose can induce ERS, and clinical studies have shown that ERS inhibitors (taurodeoxycholic acid) can relieve hyperglycemic-induced endothelial dysfunction [152]. Moreover, the overexpression of IL-12 in type 2 DM can induce ERS and OS. Moreover, the phosphorylation levels of eNOS, AKT, and AMPK are decreased, and endothelial function is abnormal, eventually leading to microcirculatory dysfunction [153]. Moreover, the inhibition of ERS protected mice from AngII-induced endothelial dysfunction, and mice treated with AngII and ERS inhibitors exhibited improved eNOS activity and increased phosphorylation. Likewise, endothelium-dependent vasodilatation was improved [154].

DM can induce chronic renal hypoxia and lead to ERS through OS, epigenetic regulation of microRNAs, overexpression of very low-density lipoprotein receptor in endothelial cells, and activation of the AKT signaling pathway. Consequently, ERS further causes damage to and apoptosis of intrinsic renal cells and renal interstitial fibrosis [155]. Renal interstitial fibrosis can impair the spread of oxygen and the oxygen supply to renal tubular and renal interstitial cells, damaging renal tubular cells. This exacerbates renal fibrosis and subsequent chronic renal hypoxia, resulting in a malignant cycle [7]. In addition, AKT mediates the activation of the PERK/eIF2α signaling pathway in ERS during hypoxia [156]. One of the stressors of ERS is hypoxia caused by microcirculatory dysfunction. However, no research has confirmed that DM can cause ERS through renal microcirculatory dysfunction and cause kidney injury.

Microcirculatory dysfunction and abnormal energy metabolism

Mitochondria are the energy production centers of cells. The kidney is an organ with a high energy requirement, so the stability of the quantity, structure, and mass of mitochondria is a precondition for maintaining kidney function [157]. In DM, an insufficient oxygen supply to tissues leads to a decrease in energy generation, which is not associated with an increase in the energy demand for glucose reabsorption in the proximal tubules of the kidney due to hyperglycemia. Moreover, OS is enhanced, the structure and function of mitochondria are damaged, ATP synthesis is further reduced, and damage to renal tissues is aggravated. Studies have shown that hypoxic stimulation can cause the mitochondria of vascular endothelial cells to swell, the mitochondrial crista to break or disappear, the matrix to become light and transparent, multiple focal vacuoles to appear in the matrix, matrix particles to be lost, and the mitochondrial membrane potential to decrease significantly [158].

At present, no research has directly explained the interaction between microcirculatory dysfunction and energy metabolism abnormalities in the pathogenesis of DN. Nevertheless, the two can be linked through the microenvironment of renal tissue with hypoxia when microcirculatory dysfunction occurs. Hypoxia can induce the expression of hundreds of genes, collectively called "hypoxia-related genes." The expression of hypoxia-related genes is regulated by transcription factors, of which hypoxia-inducible factor-1 (HIF-1) is the most important. Notably, hypoxia increases HIF-1 expression, which can induce the expression of glycolytic genes and pyruvate dehydrogenase kinase-1, subsequently inhibiting pyruvate dehydrogenase, which uses pyruvate to fuel the tricarboxylic acid cycle and causes abnormal energy metabolism [159, 160]. Previous studies have also shown that the metabolic flux of glucose and tricarboxylic acid cycle metabolites in the renal cortex of DM patients is increased [161, 162]. This may be related to mitochondrial dysfunction and DN progression [163]. Furthermore, oral administration of HIF stabilizers may reduce the mitochondrial load by normalizing the metabolism of diabetic renal tissue (downregulating fatty acid and amino acid metabolism and upregulating glycolysis), which may have a protective effect on the progression of DN [164].

Microcirculatory dysfunction and Immunologic inflammation

DN is an inflammatory disease caused by glucose and lipid metabolism disorders, with various inflammatory mediators (such as MCP-1, TGF-β, IL-6, and CRP) participating in the occurrence and development of DN [12, 165]. When the microcirculation of the kidney is disturbed, OS is increased, ROS production is increased, and excessive ROS can activate multiple signaling pathways to induce the recruitment of inflammatory cells and the release of inflammatory cytokines (such as IL, TGF-β, and MCP-1), growth factors, and transcription factors, leading to inflammation and renal fibrosis. Furthermore, OS causes significant tissue injury by promoting lipid peroxidation, DNA damage, protein modification, and mitochondrial dysfunction [166].

Both cell and animal experiments have shown that excessive infiltration of macrophages and lymphocytes plays a crucial role in DN [167, 168]. Research has also demonstrated that OS can significantly induce the recruitment of renal macrophages (compared with those in normal rats, the number of macrophages in diabetic rats is increased by approximately 4-fold) and increase the expression of monocyte chemotactic protein-1 (MCP-1) [169]. The macrophages collected in the kidney can release various cytokines, chemokines, and adhesion molecules, further activating T and B lymphocytes, mediating cellular and humoral immunity, and aggravating kidney damage. Notably, activated macrophages secrete inflammatory cytokines such as IL-6, IL-12, tumor necrosis factor-α (TNF-α), and others that act on intrinsic renal cells to promote cell hypertrophy, increase the amount of EMC produced by MCs, and inhibit the synthesis of matrix-degrading enzymes, thereby hastening the onset and progression of DN [170]. Other scholars believe that AGEs can induce endothelial cells to secrete proinflammatory cytokines (ICAM-1 and MCP-1) by activating the RhoA/ROCK signaling pathway. In doing so, it stimulates the adhesion and infiltration of macrophages, leading to renal inflammation [171], which is primarily expressed in renal monocytes, GECs, and MCs and is affected by TNF-α and IL-1, which usually regulate immune cell activity and recruitment [172, 173].

In addition, vanillic acid can improve the OS status and pathological status of renal tissue by affecting the expression of inflammatory factors (downregulating the expression of NF-κb, COX-2, and TNF-α), thereby exerting a protective effect on the kidney [174]. Among them, TNF-α plays a vital role in the pathogenesis of DN and has toxic effects on GECs and MCs. In 1989, TNF-α was shown to affect the glomerular microcirculation by stimulating MCs to produce prostaglandins and increasing endothelial cell permeability [175, 176]. In current clinical treatments, immunosuppressants and anti-inflammatory drugs can repair damaged glomerular capillaries, significantly reduce the level of urine protein, and protect renal function [17]. However, there are no scientific conclusions on whether interventions involving microcirculation changes can also change the immune state of the kidney to protect it in some way.

Collectively, microcirculatory dysfunction and immunologic inflammation can influence each other and jointly promote the occurrence and development of kidney injury in patients with DM.

Summary and prospects

The kidney is the main organ affected by hyperglycemia. In DM, damage to GECs, along with changes in hemorheology and hemodynamics induced by continuous hyperglycemia, leads to renal microcirculation dysfunction. Microcirculatory dysfunction, together with various mechanisms such as stress, immunologic inflammation, and abnormal energy metabolism induced by DM, can lead to injury of intrinsic renal cells, an increase in the ECM, thickening of the glomerular basement membrane, structural destruction of the GFB, diffuse glomerulosclerosis, and renal fibrosis. At present, specific treatments for DN are lacking. Understanding the molecular mechanism of DN through the breakthrough of microcirculatory dysfunction may provide new hope for discovering effective methods to prevent and treat DN.

Abbreviations

AGEs	Advanced glycation end products
AKT	Protein kinase B
AR	Aldose reductase
Ang II	Angiotensin II
AT1R	Angiotensin II type 1 receptor
BH_4	Tetrahydrobiopterin
CKD	Chronic kidney disease
DM	Diabetes mellitus
DN	Diabetic nephropathy
DAG	Diacylglycerol
eNOS	Endothelial nitric oxide synthase
ER	Endoplasmic reticulum
ERS	Endoplasmic reticulum stress
ESRD	End-stage renal disease
ECM	Extracellular matrix
GECs	Glomerular endothelial cells
GFB	Glomerular filtration barrier
GFAT	Glutamine: fructose-6-phosphate aminotransferase
HBP	Hexosamine biosynthesis pathway
HUVECs	Human umbilical vein endothelial cells
HIF-1	Hypoxia-inducible factor-1
ICAM-1	Intercellular adhesion molecule-1
mALB	Microalbuminuria
MDA	Malondialdehyde
MCs	Mesangial cells
MCP-1	Monocyte chemotactic protein-1
NOX4	Nicotinamide adenine dinucleotide phosphate oxidase 4
NO	Nitric oxide
O-GlcNAc	O-linked beta-N-acetylglucosamine
OS	Oxidative stress
PCs	Podocytes
PKC	Protein kinase C
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
RAGE	Receptors for advanced glycation end products
RAS	Renin–angiotensin system
TGF-β	Transforming growth factor-β
TNF-α	Tumor necrosis factor-α
UDP-GlcNAc	Uridine diphosphate N-acetylglucosamine
vWF	Von Willebrand factor

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Author contributions

Z.W. wrote the main manuscript text and contributed to conceptualization and funding acquisition. Y.G. and C.Y.Z. contributed to writing - original draft. X.R.W. prepared Figs. 1 and 2. X.H.C. contributed to writing - review & editing. X.H.Z. and W.J.G. were responsible for conceptualization, supervision, and project administration, with X.H.Z. also contributing to writing - review & editing, and W.J.G. additionally involved in funding acquisition. Specifically, X.H.Z. and W.J.G. are the corresponding authors and contributed equally to this work. All authors reviewed the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethical approval
Not applicable. This review article does not involve original research data or human/animal studies.

Competing interests
The authors declare no competing interests.

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