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Review Article

The Inflamed Endothelium in Diabetes Mellitus: Molecular Crosstalk, Vascular Complications, and Therapeutic Perspectives

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ABSTRACT

Background: Diabetes mellitus causes microvascular and macrovascular complications through interacting metabolic, oxidative, inflammatory, and vascular mechanisms. Increasing evidence identifies the endothelium as an active immunometabolic organ rather than a passive vascular barrier. Objective: To synthesize the mechanisms underlying endothelial inflammation in diabetes, its contribution to organ-specific vascular complications, and the clinical maturity of associated biomarkers and therapies. Methods: A narrative review of experimental, observational, translational, and clinical literature was undertaken. Evidence was organized around endothelial homeostasis, metabolic reprogramming, oxidative stress, inflammatory signalling, immune–endothelial crosstalk, vascular complications, biomarkers, and therapeutic strategies. Results: Hyperglycaemia, insulin resistance, dyslipidaemia, reactive oxygen species, AGE–RAGE, NF-κB, JAK/STAT, and NLRP3 signalling collectively promote endothelial activation, impaired nitric oxide bioavailability, leukocyte recruitment, barrier disruption, thrombogenicity, senescence, and defective repair. Vascular-bed-specific endothelial phenotypes contribute to diabetic kidney disease, retinopathy, cardiomyopathy, atherosclerosis, and peripheral arterial disease. Most biomarkers remain nonspecific or insufficiently validated. SGLT2 inhibitors and GLP-1 receptor agonists have established cardiorenal benefits, whereas direct anti-inflammatory, antioxidant, glycocalyx-targeted, phytochemical, and nanomedicine approaches remain investigational. Conclusion: Endothelial inflammation provides an integrated framework for diabetic vascular injury, but biomarker-guided and endothelial-targeted management requires prospective clinical validation. Keywords: Diabetes mellitus; Endothelial inflammation; Oxidative stress; Immune–endothelial crosstalk; Vascular complications; Biomarkers

INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder associated with substantial clinical, societal, and economic burden. Its consequences extend well beyond impaired glucose regulation because prolonged metabolic disturbance progressively damages the vascular system and contributes to disability, organ failure, and premature mortality. The cost of managing diabetes is therefore driven not only by long-term glycaemic treatment but also by the prevention and management of its vascular complications (1).

Diabetic vascular disease includes microvascular complications, such as nephropathy, retinopathy, and neuropathy, and macrovascular disorders, including coronary artery disease, cerebrovascular disease, and peripheral arterial disease. Although these complications affect anatomically distinct organs, they share important pathological features involving oxidative stress, inflammatory activation, impaired vascular repair, and disruption of endothelial homeostasis. Diabetes-associated vascular inflammation

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contributes to atherosclerotic plaque instability (2), while inflammatory and fibrotic pathways accelerate diabetic kidney disease (3). Diabetic retinopathy remains a major microvascular complication for which improved risk prediction is required (4), and experimental evidence demonstrates that oxidative and inflammatory injury also contributes to diabetic myocardial damage (5). In the peripheral circulation, impaired nitric oxide signalling and defective vascular repair adversely affect wound healing and increase the risk of chronic diabetic ulcers and related complications (6).

The vascular endothelium is a metabolically active and functionally heterogeneous cellular interface that regulates vascular tone, permeability, haemostasis, leukocyte trafficking, angiogenesis, and tissue repair. Under physiological conditions, endothelial cells maintain a vasodilatory, antithrombotic, anti-inflammatory, and selectively permeable vascular environment. Diabetes progressively disrupts this phenotype through the combined effects of hyperglycaemia, insulin resistance, dyslipidaemia, mitochondrial dysfunction, and chronic low-grade inflammation. These disturbances increase reactive oxygen species production, reduce nitric oxide bioavailability, damage the endothelial glycocalyx, and activate interconnected inflammatory pathways. Human evidence from diabetic nephropathy has linked oxidative stress with increased peroxidasin and nuclear factor-κB activity (7), while experimental findings indicate that diabetes may amplify vascular inflammation through immune pathways such as the CD137 ligand–CD137 axis (8). Regulatory T-cell–endothelial interactions further illustrate that vascular inflammation is governed by reciprocal communication between endothelial and immune cells rather than by endothelial injury alone (9).

These observations support an important distinction between endothelial dysfunction and endothelial inflammation. Endothelial dysfunction primarily refers to impaired vascular reactivity, reduced nitric oxide bioavailability, and loss of normal vasodilatory capacity. The inflamed endothelium represents a broader immunometabolic phenotype characterized by sustained inflammatory signalling, adhesion-molecule expression, immune-cell recruitment, barrier disruption, prothrombotic activity, metabolic reprogramming, and impaired vascular repair. Persistent activation of the advanced glycation end product–receptor for advanced glycation end products axis, nuclear factor-κB, mitogen-activated protein kinase/c-Jun N-terminal kinase, Janus kinase/signal transducer and activator of transcription signalling, and the NLRP3 inflammasome establishes interacting feed-forward mechanisms that sustain endothelial injury. Rather than functioning as independent pathways, these networks converge on oxidative stress, cytokine production, leukocyte adhesion, endothelial senescence, and progressive vascular remodelling.

The biological response of the endothelium is not uniform throughout the circulation. Endothelial cells exhibit tissue-specific structural, transcriptional, and metabolic phenotypes that influence their susceptibility to diabetic injury. Fenestrated glomerular endothelial cells, tightly connected retinal and cerebral microvascular endothelial cells, coronary microvascular endothelial cells, and peripheral vascular endothelial cells therefore respond differently to similar systemic metabolic disturbances. Single-cell transcriptomic analysis of diabetic foot ulcers has demonstrated substantial endothelial heterogeneity and identified distinct cellular states associated with impaired healing (10). This heterogeneity helps explain why common metabolic and inflammatory pathways produce different clinical manifestations across the kidney, retina, myocardium, arterial wall, and peripheral tissues. Nevertheless, existing literature frequently examines endothelial dysfunction, metabolic stress, inflammatory signalling, or individual organ complications separately, leaving the molecular connections among these processes insufficiently integrated.

The therapeutic implications of this concept extend beyond glucose reduction alone. Sodium–glucose cotransporter-2 inhibitors have demonstrated cardiovascular and vascular benefits that may involve improvements in oxidative stress, inflammation, endothelial function, and vascular remodelling (11). Glucagon-like peptide-1 receptor agonists and their combination with sodium–glucose cotransporter-2 inhibitors may provide complementary metabolic, renal, and cardiovascular protection (12). Other

approaches, including inflammasome inhibition, glycocalyx preservation, targeted antioxidant therapy, extracellular-vesicle-based interventions, and nanomaterial-assisted drug delivery, remain at varying stages of experimental and clinical development (13). These strategies should not be considered equivalent: some are supported by cardiovascular or renal outcome evidence, whereas others remain mechanistically promising but clinically unvalidated.

Accordingly, this narrative review critically synthesizes the molecular and cellular mechanisms that transform the diabetic endothelium from a homeostatic vascular interface into a persistently inflamed and dysfunctional phenotype. It examines the interactions among metabolic stress, oxidative injury, inflammatory signalling, and immune–endothelial communication; evaluates how endothelial heterogeneity contributes to organ-specific vascular complications; and reviews biomarkers of endothelial activation and injury. It also distinguishes established vascular-protective treatments from investigational endothelial-directed interventions and identifies the principal barriers that must be addressed before endothelial biomarkers and targeted therapies can be incorporated into routine clinical practice.

MATERIALS AND METHODS

This article was developed as a narrative review of the molecular, cellular, translational, and clinical literature concerning endothelial inflammation in diabetes mellitus. The evidence base comprised the publications included in the manuscript bibliography, which span experimental, observational, translational, and clinical research published between 2012 and 2026. The scope of the review included endothelial homeostasis, diabetes-associated metabolic stress, oxidative injury, inflammatory signalling, immune–endothelial communication, organ-specific vascular complications, biomarkers of endothelial activation and injury, and therapeutic strategies with potential endothelial effects.

Publications were considered relevant when they directly addressed at least one of the principal review domains: normal endothelial physiology; hyperglycaemia-, insulin resistance-, or dyslipidaemia-associated endothelial injury; AGE–RAGE, NF-κB, MAPK/JNK, JAK/STAT, or NLRP3 signalling; endothelial metabolic reprogramming; leukocyte–endothelial interactions; diabetic nephropathy, retinopathy, cardiomyopathy, atherosclerosis, or peripheral arterial disease; endothelial or inflammatory biomarkers; or pharmacological and emerging interventions affecting vascular homeostasis. Evidence relating to general inflammatory disorders was used only when it clarified a biologically relevant endothelial pathway and was not treated as direct evidence of therapeutic efficacy in diabetes. Human studies and authoritative clinical reviews were prioritized for clinical and prognostic claims, whereas cellular and animal studies were used primarily to explain molecular mechanisms and generate translational hypotheses.

Relevant information was narratively extracted and organized according to the biological pathway, endothelial function, vascular bed, diabetic complication, biomarker category, therapeutic target, and level of translational maturity. Mechanistic findings were synthesized by identifying points of convergence among metabolic abnormalities, reactive oxygen species generation, nitric oxide impairment, inflammatory transcription, inflammasome activation, immune-cell recruitment, endothelial barrier disruption, thrombogenicity, senescence, and defective vascular repair. Organ-specific evidence was interpreted in relation to endothelial heterogeneity rather than assuming a uniform vascular response across tissues. Biomarkers were evaluated according to their biological specificity, specimen source, relationship to disease activity, and potential diagnostic or prognostic role. Therapeutic interventions were categorized as established treatments with clinical vascular-outcome evidence, repurposed or investigational anti-inflammatory approaches, adjunctive antioxidant or phytochemical strategies, and predominantly preclinical precision therapies.

No quantitative pooling or meta-analysis was undertaken because the included literature was heterogeneous with respect to study design, patient population, experimental model, vascular bed,

exposure definition, intervention, and outcome measurement. To limit overinterpretation, evidence from experimental models was distinguished from direct human evidence, associative biomarker findings were not treated as proof of causation, and improvements in molecular or endothelial surrogate measures were not considered equivalent to reductions in clinical vascular events. Particular attention was given to separating endothelial-specific markers from nonspecific indicators of systemic inflammation and to distinguishing direct endothelial effects of treatment from vascular benefits mediated through improved glycaemia, blood pressure, body weight, renal haemodynamics, or systemic inflammatory control.

The synthesis was structured around five interconnected domains: maintenance and loss of endothelial homeostasis; molecular mechanisms of endothelial inflammation; immune and vascular-cell crosstalk; organ-specific diabetic vascular injury; and the clinical translation of biomarkers and endothelial-directed therapies. Findings were integrated descriptively to identify established mechanisms, areas supported primarily by preclinical evidence, unresolved inconsistencies, and priorities for future research. As the review used previously published literature and involved no collection of primary human or animal data, institutional ethics approval and individual informed consent were not required.

Endothelial Homeostasis and Its Disruption in Diabetes

The vascular endothelium is a heterogeneous and metabolically active cellular interface that coordinates vascular tone, permeability, haemostasis, inflammatory surveillance, angiogenesis, and tissue repair. Preservation of these functions depends on the coordinated production of nitric oxide, prostacyclin, anticoagulant mediators, junctional proteins, and glycocalyx components. Physical activity and other vascular-protective interventions may improve endothelial function by enhancing nitric oxide signalling, reducing oxidative stress, and restoring vascular responsiveness in metabolic and cardiovascular disorders (14). Conversely, persistent metabolic stress promotes endothelial senescence, characterized by reduced proliferative capacity, altered secretory activity, impaired repair, and acquisition of a pro-inflammatory phenotype (15).

Endothelial responses differ substantially among vascular beds. In the kidney, glomerular endothelial cells interact closely with podocytes and tubular epithelial cells, and disruption of this cellular communication contributes to albuminuria, inflammation, and progressive diabetic kidney injury (16). Nitric oxide produced by endothelial nitric oxide synthase remains central to vasodilation, inhibition of platelet activation, suppression of leukocyte adhesion, and maintenance of vascular integrity (17). The protective influence of nitric oxide is opposed by excessive endothelin-1 and angiotensin II signalling, which favour vasoconstriction, oxidative stress, inflammation, and vascular remodelling (18). Angiotensin II may also increase endothelial sodium–glucose cotransporter expression and promote cellular senescence, whereas sodium–glucose cotransporter-2 inhibition may attenuate some of these adverse vascular effects (19).

Barrier integrity depends on endothelial junctional proteins, particularly vascular endothelial cadherin, together with claudins, occludins, zonula occludens proteins, and the endothelial glycocalyx. Disruption of vascular endothelial cadherin alters endothelial cohesion and permeability, thereby facilitating inflammatory-cell migration and tissue oedema (20). Glycocalyx degradation removes an important anti-adhesive and mechanosensitive surface layer, increasing vascular permeability and exposing endothelial adhesion receptors to circulating leukocytes and platelets (21). Endothelial haemostatic regulation also involves fibrinolytic and angiogenic mechanisms, including annexin A2-dependent plasminogen activation and prostacyclin-mediated vascular responses (22,23). Loss of the normal antithrombotic phenotype can transform endothelial cells into a procoagulant surface, particularly under conditions of apoptosis, oxidative injury, or drug-induced cellular toxicity (24).

Endothelial cells also function as innate immune sensors. Damage-associated molecular patterns generated during metabolic and tissue injury activate pattern-recognition pathways that promote

vascular inflammation and immunothrombosis (25). Under physiological laminar flow, Krüppel-like factors 2 and 4 promote endothelial nitric oxide synthase, thrombomodulin, and antioxidant gene expression while suppressing inflammatory transcription (26). In contrast, disturbed or oscillatory flow reprograms endothelial cells toward oxidative, adhesive, and atherogenic states (27). Diabetes intensifies this susceptibility by combining abnormal metabolic exposure with impaired mechanotransduction, reduced nitric oxide bioavailability, glycocalyx loss, senescence, and defective endothelial repair.

Integrated Molecular Mechanisms of the Inflamed Endothelium

Diabetic endothelial inflammation arises from the convergence of hyperglycaemia, insulin resistance, dyslipidaemia, oxidative stress, and inflammatory signalling rather than from a single initiating pathway. Chronic glucose excess increases mitochondrial reactive oxygen species generation, advanced glycation end-product formation, endothelial nitric oxide synthase uncoupling, and activation of redox-sensitive transcriptional pathways. These processes impair vasodilation, increase endothelial permeability, promote leukocyte adhesion, and establish a prothrombotic vascular environment that contributes to both microvascular and macrovascular disease (28).

Inflammatory cytokines amplify this metabolic injury. Interleukin-1β, interleukin-6, interleukin-17, interleukin-18, tumour necrosis factor-α, and related mediators influence endothelial activation, oxidative stress, leukocyte recruitment, and vascular remodelling, although their effects vary according to disease context and vascular bed (29). Endothelial metabolic reprogramming further sustains inflammation by altering glycolytic flux, mitochondrial function, substrate utilization, and cellular redox balance. Evidence from vascular-remodelling models indicates that metabolic and inflammatory signalling are closely interconnected rather than operating as independent responses (30). More specifically, endothelial metabolic reprogramming has been associated with reduced bioenergetic flexibility, impaired angiogenesis, senescence, and chronic inflammatory activation (31).

The advanced glycation end product–receptor for advanced glycation end products axis serves as a major bridge between prolonged metabolic exposure and inflammatory transcription. Ligand binding to the receptor for advanced glycation end products increases reactive oxygen species production and activates nuclear factor-κB, thereby enhancing cytokine, chemokine, adhesion-molecule, and profibrotic gene expression. Persistent receptor activation creates a feed-forward loop in which oxidative stress promotes additional advanced glycation end-product formation and inflammatory signalling (32).

Janus kinase/signal transducer and activator of transcription signalling contributes to sustained endothelial responses to cytokines, particularly during prolonged rather than immediate inflammatory activation. This pathway may maintain interferon-responsive and cytokine-amplifying transcriptional programmes even when early nuclear factor-κB activity has declined (33). The NLRP3 inflammasome provides another point of convergence among mitochondrial dysfunction, reactive oxygen species, cellular stress, and innate immune activation. NLRP3 assembly promotes caspase-1 activation and maturation of interleukin-1β and interleukin-18, thereby worsening endothelial permeability, inflammation, and vascular dysfunction (34).

These signalling pathways are reinforced by immune–endothelial interactions. Endothelial expression of intercellular adhesion molecule-1, vascular cell adhesion molecule-1, E-selectin, chemokines, and cytokines promotes monocyte, neutrophil, and lymphocyte adhesion and transendothelial migration. Recruited leukocytes subsequently release reactive oxygen species, proteases, cytokines, and tissue-remodelling mediators, further activating the vascular wall. This reciprocal communication is particularly relevant to atherosclerotic lesion formation, in which endothelial activation controls the location, intensity, and duration of leukocyte recruitment (35). The inflamed endothelium should therefore be understood as an integrated phenotype involving metabolic reprogramming, oxidative injury, altered vasomotor function, barrier disruption, innate immune activation, leukocyte trafficking, thrombogenicity, senescence, and impaired vascular repair.

Organ-Specific Vascular Complications

The consequences of endothelial inflammation vary according to the structural and metabolic characteristics of individual vascular beds. Coronary microvascular dysfunction in diabetes reflects reduced nitric oxide availability, oxidative stress, impaired vasodilation, capillary rarefaction, inflammatory activation, and altered myocardial perfusion. These abnormalities may develop before obstructive epicardial coronary disease and contribute to exercise intolerance, myocardial dysfunction, and heart failure risk (36).

In diabetic kidney disease, glomerular endothelial injury is an early component of disease progression. Glycocalyx loss, impaired nitric oxide signalling, increased permeability, inflammatory-cell recruitment, and profibrotic communication among glomerular endothelial cells, podocytes, mesangial cells, and tubular epithelial cells promote albuminuria, glomerulosclerosis, and progressive loss of renal function (37). Endothelial inflammation is therefore not merely a consequence of advanced nephropathy but part of the cellular environment that facilitates its initiation and progression.

Diabetic heart disease encompasses both accelerated atherosclerotic disease and myocardial injury that may occur independently of obstructive coronary artery disease. Endothelial activation contributes to lipid entry, leukocyte recruitment, foam-cell formation, plaque progression, and arterial remodelling. Within the myocardium, microvascular dysfunction, oxidative stress, inflammation, fibrosis, and impaired perfusion contribute to ventricular stiffness and contractile dysfunction (38). These mechanisms support separating diabetic cardiomyopathy from atherosclerosis while recognizing that both are influenced by endothelial inflammation.

The retinal microvasculature is particularly sensitive to endothelial barrier disruption. Oxidative stress, inflammatory signalling, vascular endothelial growth factor activity, leukostasis, and loss of endothelial–pericyte support increase blood–retinal barrier permeability and capillary instability. Progressive capillary closure produces retinal ischaemia and stimulates pathological neovascularization, which can lead to visual impairment and blindness (39).

In peripheral arterial disease, diabetes combines accelerated atherosclerosis with impaired microvascular repair, reduced angiogenic responsiveness, endothelial dysfunction, thrombosis, and defective wound healing. These changes reduce tissue perfusion, increase susceptibility to diabetic foot ulceration, and contribute to infection, tissue necrosis, and amputation risk (40). Across these complications, shared inflammatory pathways interact with vascular-bed-specific endothelial phenotypes, explaining why a common systemic metabolic disorder produces clinically distinct patterns of organ injury.

Biomarkers of Endothelial Inflammation

Biomarkers associated with diabetic vascular complications include systemic inflammatory mediators, endothelial adhesion molecules, vasoactive factors, angiogenic proteins, oxidative markers, and tissue-remodelling enzymes. In diabetic kidney disease, tumour necrosis factor-α, interleukin-6, interleukin-1β, monocyte chemoattractant protein-1, intercellular adhesion molecule-1, vascular cell adhesion molecule-1, E-selectin, high-sensitivity C-reactive protein, vascular endothelial growth factor, and endothelin-1 have been linked to inflammatory activation, fibrosis, endothelial dysfunction, and albuminuria (41). Other biochemical markers may reflect renal injury or extracellular-matrix remodelling, but their diagnostic and prognostic roles remain insufficiently standardized (42).

Cardiovascular studies have evaluated inflammatory cytokines, adhesion molecules, oxidized low-density lipoprotein, C-reactive protein, monocyte chemoattractant protein-1, and endothelin-1 as indicators of vascular inflammation and endothelial dysfunction in diabetes (43). Experimental evidence also suggests that prolonged hyperglycaemia can alter myocardial transcriptional and epigenetic

regulation, supporting the concept of metabolic memory and persistent cardiovascular injury despite later glycaemic improvement (44).

In diabetic retinopathy, vascular endothelial growth factor, intercellular adhesion molecule-1, vascular cell adhesion molecule-1, interleukin-6, interleukin-8, tumour necrosis factor-α, and monocyte chemoattractant protein-1 have been measured in serum, aqueous humour, and vitreous humour (45,46). Local ocular concentrations may more directly reflect retinal disease activity than circulating levels, but their invasive collection limits routine clinical use. In peripheral arterial disease and diabetic foot disease, circulating inflammatory markers, matrix metalloproteinase-9, endothelial adhesion molecules, vascular endothelial growth factor, and wound-fluid mediators have been investigated as indicators of inflammation, angiogenic impairment, and healing potential (47,48).

Despite biological plausibility, most proposed biomarkers have limited endothelial specificity. C-reactive protein, interleukin-6, and tumour necrosis factor-α may increase because of obesity, renal dysfunction, infection, systemic atherosclerosis, or other inflammatory conditions. Adhesion molecules and vasoactive mediators may more directly reflect endothelial activation but remain influenced by comorbidity, medication use, assay platform, and sample timing. Consequently, individual biomarkers currently provide insufficient specificity for routine diagnosis or treatment selection. Multimarker panels integrated with clinical characteristics, vascular imaging, endothelial-function testing, and longitudinal outcomes may have greater translational value than isolated analytes. Table 1 summarizes the principal biomarker domains, specimen sources, biological interpretations, and current limitations.

Table 1. Biomarkers Evaluated in Major Diabetic Vascular Complications

Diabetic complication	Biomarker domain	Representative biomarkers	Specimen source	Biological interpretation	Current clinical status and limitations	REFERENCES
Diabetic kidney disease	Systemic inflammation	TNF-α, IL-6, IL-1β, hs-CRP, MCP-1/CCL2	Serum, plasma, urine	Inflammatory activation, leukocyte recruitment, renal injury and fibrosis	Mostly research or prognostic markers; limited specificity because values are affected by renal function, obesity and infection	(41,42)
Diabetic kidney disease	Endothelial activation and vasoactive dysfunction	ICAM-1, VCAM-1, E-selectin, VEGF, endothelin-1	Serum, plasma, urine	Endothelial activation, altered permeability, glomerular injury and vascular dysregulation	Potentially more endothelial-related than general cytokines, but assay thresholds and longitudinal predictive value remain insufficiently standardized	(41,42)
Diabetic cardiomyopathy and atherosclerosis	Systemic and vascular inflammation	TNF-α, IL-6, IL-1β, hs-CRP, MCP-1	Serum, plasma	Chronic inflammation, leukocyte recruitment and plaque progression	Associated with risk but not specific to diabetic endothelial injury	(43,44)
Diabetic cardiomyopathy and atherosclerosis	Endothelial and oxidative injury	ICAM-1, VCAM-1, oxidized LDL, endothelin-1	Serum, plasma	Endothelial activation, oxidative lipid injury, impaired vasoregulation and arterial remodelling	Useful for mechanistic and risk research; limited routine standardization and uncertain incremental value over conventional risk factors	(43,44)
Diabetic retinopathy	Angiogenesis and barrier disruption	VEGF, ICAM-1, VCAM-1	Serum, vitreous humour, aqueous humour	Blood–retinal barrier dysfunction, leukostasis and neovascularization	Local ocular levels may reflect disease activity but require invasive sampling; circulating measurements have variable specificity	(45,46)
Diabetic retinopathy	Inflammation and chemotaxis	IL-6, IL-8, TNF-α, MCP-1	Serum, vitreous humour, aqueous humour	Retinal inflammation and immune-cell recruitment	Mainly investigational; affected by disease stage, treatment exposure and sampling compartment	(45,46)
Peripheral arterial disease and diabetic foot disease	Systemic inflammation	TNF-α, IL-6, CRP	Serum, plasma	Chronic inflammation and adverse wound environment	Widely measurable but nonspecific; elevation may reflect infection or tissue necrosis	(47,48)
Peripheral arterial disease and diabetic foot disease	Endothelial, angiogenic and remodelling markers	ICAM-1, VCAM-1, E-selectin, VEGF, MMP-9	Serum, plasma, wound exudate	Endothelial activation, impaired angiogenesis, matrix degradation and delayed healing	Promising for prognostic panels, but collection methods, thresholds and outcome associations require validation	(47,48)

TNF-α: tumour necrosis factor-α; IL: interleukin; hs-CRP: high-sensitivity C-reactive protein; MCP-1: monocyte chemoattractant protein-1; CCL2: C-C motif chemokine ligand 2; ICAM-1: intercellular adhesion molecule-1; VCAM-1: vascular cell adhesion molecule-1; VEGF: vascular endothelial growth factor; LDL: low-density lipoprotein; MMP-9: matrix metalloproteinase-9.

Therapeutic Perspectives

Treatment of diabetic vascular disease continues to depend primarily on comprehensive control of glycaemia, blood pressure, lipids, smoking exposure, kidney disease, and other conventional cardiovascular risk factors. Metformin remains an established glucose-lowering therapy, whereas sodium–glucose cotransporter-2 inhibitors, glucagon-like peptide-1 receptor agonists, and dipeptidyl peptidase-4 inhibitors differ substantially in their cardiovascular, renal, metabolic, and endothelial

evidence profiles (49). Sodium–glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists have the strongest contemporary evidence for vascular and cardiorenal benefit, although their effects cannot be attributed exclusively to direct endothelial actions. Improvements in haemodynamics, body weight, renal function, glycaemia, oxidative stress, and systemic inflammation may collectively contribute to the observed outcomes (50). Comparative evidence suggests that these drug classes should not be treated as interchangeable, because their cardiovascular and metabolic effects vary according to patient characteristics, background treatment, and clinical outcome (51).

Anti-inflammatory strategies offer a biologically plausible approach but remain incompletely established for diabetic endothelial disease. Colchicine has demonstrated anti-inflammatory and cardioprotective effects in cardiovascular settings, yet its specific role in preventing diabetes-related endothelial complications requires further evaluation (52). Janus kinase inhibition can suppress cytokine-dependent inflammatory signalling, but systemic immunosuppression, infection risk, thrombotic concerns, and the absence of diabetes-specific endothelial outcome trials limit routine application (53).

Antioxidants such as N-acetylcysteine, alpha-lipoic acid, vitamins C and E, and melatonin may reduce oxidative injury or improve surrogate measures in experimental or selected clinical settings. However, the biological complexity of reactive oxygen species signalling and inconsistent translation from molecular improvement to clinical vascular benefit have prevented antioxidants from becoming definitive endothelial-directed therapies (54).

Natural compounds, including curcumin, resveratrol, and berberine, have demonstrated anti-inflammatory, antioxidant, and endothelial effects in experimental studies. Curcumin may influence nuclear factor-κB, oxidative stress, and endothelial nitric oxide signalling, but bioavailability and heterogeneity of formulations complicate clinical interpretation (55). Resveratrol has protected cultured endothelial cells against tumour necrosis factor-α-mediated injury through sirtuin-1-related suppression of nuclear factor-κB and p38 mitogen-activated protein kinase signalling (56). Berberine has shown broad metabolic and cardiovascular actions, but dose standardization, drug interactions, formulation quality, and limited hard-outcome evidence remain important barriers (57).

Table 2. Therapeutic Strategies Relevant to Endothelial Inflammation in Diabetes Mellitus

Therapeutic category	Representative interventions	Principal targets or mechanisms	Evidence maturity	Potential endothelial or vascular effects	Important limitations	REFERENCES
Glucose-lowering therapies with established cardiorenal relevance	SGLT2 inhibitors, GLP-1 receptor agonists	SGLT2 inhibition, GLP-1 receptor signalling, metabolic and haemodynamic modulation	Clinical outcome-supported, although endothelial mechanisms are partly indirect	Reduced oxidative stress and inflammation, improved vascular function, reduced cardiorenal risk	Benefits cannot be attributed solely to direct endothelial action; class and patient effects vary	(50,51)
Established glucose-lowering therapies with mainly surrogate endothelial evidence	Metformin, DPP-4 inhibitors	AMPK activation, incretin-related signalling and glycaemic control	Established metabolic treatment; endothelial evidence varies	Potential improvement in nitric oxide availability, inflammation and oxidative balance	Limited direct evidence that endothelial surrogate improvements independently reduce vascular events	(49–51)
Anti-inflammatory pharmacotherapy	Colchicine	Microtubule disruption and suppression of inflammatory-cell activation	Cardiovascular evidence available; diabetes-specific endothelial role remains investigational	Reduced inflammatory signalling and leukocyte activity	Gastrointestinal intolerance, drug interactions and uncertain diabetes-specific benefit	(52)
Cytokine-signalling inhibition	JAK inhibitors	JAK/STAT pathway inhibition	Established in selected immune diseases; experimental for diabetic vascular prevention	Reduced cytokine amplification and endothelial inflammatory transcription	Infection, thrombotic and systemic immunosuppressive risks; no routine diabetes indication	(53)
Antioxidant approaches	N-acetylcysteine, alpha-lipoic acid, vitamins C and E, melatonin	Reactive oxygen species reduction and antioxidant pathway support	Mixed experimental and limited clinical evidence	Potential restoration of redox balance and nitric oxide bioavailability	Inconsistent clinical outcomes, variable dosing and inability to target specific reactive oxygen species sources	(54)
Phytochemical and natural-product strategies	Curcumin, resveratrol, berberine	NF-κB, sirtuin-1, p38 MAPK, oxidative and metabolic pathways	Predominantly experimental and early clinical evidence	Anti-inflammatory, antioxidant and potential endothelial-protective effects	Variable formulation, bioavailability, dose standardization, product quality and limited hard-outcome data	(55–57)
Glycocalyx-preserving approaches	Strategies intended to reduce glycocalyx	Endothelial surface-layer integrity, permeability and mechanotransduction	Mechanistic and early translational evidence	Reduced permeability, leukocyte adhesion and	Lack of validated clinical endpoints and absence of	(21)

Therapeutic category	Representative interventions	Principal targets or mechanisms	Evidence maturity	Potential endothelial or vascular effects	Important limitations	REFERENCES
	degradation or promote restoration			endothelial exposure to inflammatory injury	established diabetes-specific therapies	
Targeted and nanomaterial-assisted delivery	Nanomaterial-based vascular drug-delivery platforms	Enhanced tissue targeting and controlled drug release	Preclinical and early translational	Potential delivery of anti-inflammatory or antioxidant agents to vascular tissues	Toxicity, biodistribution, immunogenicity, reproducibility, manufacturing and regulatory concerns	(13)

Glycocalyx-preserving strategies are mechanistically attractive because glycocalyx loss occurs early in vascular injury and contributes to permeability, inflammation, and leukocyte adhesion (21). Nevertheless, specific glycocalyx-directed treatments have not yet reached routine diabetes care. Nanomaterial-assisted delivery may improve vascular targeting and reduce systemic exposure, but concerns regarding biodistribution, toxicity, manufacturing consistency, immunogenicity, and regulatory oversight remain unresolved (13). Therapeutic development should therefore distinguish interventions supported by clinical outcome evidence from those supported only by surrogate, experimental, or theoretical findings. Table 2 classifies the principal therapeutic approaches according to their evidence maturity, potential endothelial effects, and translational limitations.

DISCUSSION

This narrative review identifies endothelial inflammation as an integrated pathological phenotype through which metabolic abnormalities are translated into vascular injury in diabetes mellitus. The principal synthesis is that hyperglycaemia, insulin resistance, dyslipidaemia, mitochondrial dysfunction, and disturbed haemodynamic signalling converge on oxidative stress, reduced nitric oxide bioavailability, inflammatory transcription, inflammasome activation, leukocyte recruitment, barrier disruption, thrombogenicity, senescence, and impaired repair. These abnormalities do not occur as isolated molecular events. Instead, they form mutually reinforcing networks that progressively transform the endothelium from a vasoprotective interface into an active regulator of chronic vascular inflammation.

The distinction between endothelial dysfunction and the inflamed endothelium is clinically and conceptually important. Endothelial dysfunction traditionally emphasizes impaired vasodilation and reduced nitric oxide activity, whereas endothelial inflammation incorporates immunological, metabolic, barrier, haemostatic, and reparative abnormalities. This broader framework better explains why restoration of vascular reactivity alone may be insufficient to prevent progressive organ injury. Glycocalyx degradation, adhesion-molecule expression, cytokine amplification, inflammasome activity, endothelial senescence, and leukocyte recruitment may persist even when individual metabolic indicators improve. The concept of metabolic memory further suggests that previous hyperglycaemic exposure can produce sustained transcriptional and epigenetic effects that are not immediately reversed by subsequent glycaemic control (44).

The available evidence also demonstrates that endothelial injury is strongly dependent on vascular-bed biology. Glomerular endothelial cells operate within a specialized filtration barrier and interact continuously with podocytes and tubular cells, whereas retinal endothelial cells form the blood–retinal barrier and depend on close endothelial–pericyte communication. Coronary microvascular endothelial cells regulate myocardial perfusion and substrate delivery, while peripheral endothelial cells are essential for collateral formation, wound repair, and tissue viability. Consequently, the same systemic metabolic disturbance can produce albuminuria in the kidney, leakage and capillary closure in the retina, impaired perfusion and myocardial dysfunction in the heart, or ulceration and tissue loss in the lower limb. Endothelial heterogeneity therefore limits the usefulness of treating diabetic vascular disease as a uniform biological process.

Most mechanistic evidence supports a central role for reactive oxygen species, nuclear factor-κB, receptor for advanced glycation end products signalling, cytokine pathways, and the NLRP3 inflammasome. However, the strength of evidence differs among pathways. Some mechanisms are supported by

convergent cellular, animal, and human observations, whereas others remain dependent on experimental models or indirect evidence from non-diabetic inflammatory conditions. Experimental demonstration of pathway activation does not necessarily establish that selective inhibition will improve clinical outcomes. Redundancy among inflammatory pathways may also allow one network to compensate when another is pharmacologically inhibited.

The biomarker literature illustrates this translational gap. Numerous inflammatory cytokines, adhesion molecules, vasoactive mediators, angiogenic factors, and tissue-remodelling enzymes are associated with diabetic vascular complications. Nevertheless, association does not establish endothelial specificity, temporal precedence, or incremental clinical value. Commonly investigated biomarkers such as C-reactive protein, interleukin-6, and tumour necrosis factor-α may reflect obesity, infection, renal impairment, systemic atherosclerosis, or generalized inflammation rather than endothelial injury itself. More endothelial-related markers, including intercellular adhesion molecule-1, vascular cell adhesion molecule-1, E-selectin, endothelin-1, and glycocalyx products, may still vary according to medication exposure, assay method, sample timing, and disease stage. Single-marker strategies are therefore unlikely to provide adequate diagnostic or prognostic performance.

A more promising approach may involve multimarker models that combine systemic inflammatory markers with endothelial-specific proteins, functional vascular testing, imaging findings, genomic or transcriptomic signatures, and established clinical risk variables. Such models require prospective validation to determine whether they predict complications beyond conventional measures such as glycated haemoglobin, blood pressure, lipid profile, albuminuria, estimated glomerular filtration rate, smoking status, and duration of diabetes. Biomarker studies should also demonstrate that test results can alter treatment decisions or improve patient outcomes before routine implementation is recommended.

The therapeutic findings require similarly cautious interpretation. Sodium–glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists have demonstrated important cardiovascular and renal benefits, but these outcomes arise through multiple metabolic, haemodynamic, renal, inflammatory, and vascular mechanisms. It would therefore be inappropriate to describe them as selective endothelial therapies. Metformin and dipeptidyl peptidase-4 inhibitors may improve selected endothelial surrogate measures, but improvement in a laboratory or physiological marker is not equivalent to prevention of vascular events. Future studies should distinguish direct endothelial effects from improvements mediated through weight reduction, glycaemic control, blood-pressure lowering, renal haemodynamics, or systemic inflammatory modulation.

Anti-inflammatory and antioxidant treatments remain biologically attractive but clinically uncertain. Broad cytokine or Janus kinase inhibition may reduce endothelial activation but can also impair host defence and increase systemic adverse effects. Antioxidants have often demonstrated favourable molecular findings without producing consistent reductions in major vascular events. One explanation is that reactive oxygen species also participate in physiological signalling, meaning that non-selective antioxidant suppression may fail to correct the specific intracellular source or timing of oxidative injury. Targeted strategies that inhibit pathological reactive oxygen species production or restore endogenous antioxidant regulation may be more effective than indiscriminate scavenging.

Natural products such as curcumin, resveratrol, and berberine require particularly careful interpretation. Their biological effects are plausible, but experimental findings are frequently based on concentrations, formulations, or exposure conditions that are difficult to reproduce clinically. Variability in bioavailability, purity, dosage, manufacturing quality, and concomitant medication use further limits direct translation. These compounds should therefore be presented as investigational adjuncts rather than established treatments for diabetic endothelial disease.

Emerging approaches, including glycocalyx restoration and targeted drug-delivery systems, may overcome some limitations of systemic therapy. Preserving the endothelial glycocalyx could theoretically improve vascular permeability, mechanotransduction, and resistance to leukocyte and platelet adhesion. Nanomaterial-based platforms may facilitate tissue-specific delivery of anti-inflammatory, antioxidant, or gene-regulatory interventions. However, both strategies require standardized outcome measures, detailed toxicity assessment, reproducible manufacturing, and evidence of long-term clinical benefit before routine application.

This review has several limitations. It was conducted as a narrative rather than systematic review and did not include quantitative pooling, formal risk-of-bias assessment, or certainty grading. The included literature was heterogeneous with respect to diabetes type, disease duration, experimental model, vascular bed, study design, treatment exposure, and outcome definition. Some mechanistic concepts were informed by non-diabetic vascular or inflammatory research when direct diabetes-specific evidence was limited. The narrative synthesis may therefore be influenced by publication availability and author selection. In addition, the absence of standardized definitions of endothelial inflammation complicates comparisons among studies.

Future research should establish consensus definitions and core outcome sets for diabetic endothelial inflammation. Longitudinal studies should determine the temporal relationship among metabolic abnormalities, endothelial activation, biomarker changes, and clinical organ injury. Vascular-bed-specific single-cell and spatial analyses may identify endothelial subpopulations that are particularly susceptible to diabetes and reveal targets that are obscured in bulk tissue studies. Clinical trials should include prespecified endothelial outcomes, distinguish type 1 from type 2 diabetes, account for sex and comorbidity, and determine whether biomarker-guided or endothelial-targeted strategies improve outcomes beyond comprehensive conventional risk-factor management.

CONCLUSION

Diabetes mellitus promotes an inflamed endothelial phenotype through the interacting effects of metabolic stress, oxidative injury, impaired nitric oxide signalling, inflammatory transcription, inflammasome activation, immune-cell recruitment, barrier disruption, thrombogenicity, senescence, and defective vascular repair. These shared mechanisms are modified by vascular-bed-specific endothelial biology and contribute to the distinct manifestations of diabetic kidney disease, retinopathy, cardiomyopathy, atherosclerosis, and peripheral arterial disease. Although numerous biomarkers and endothelial-directed therapies are biologically promising, most lack sufficient specificity, standardization, prospective validation, or clinical outcome evidence for routine use. Current management should therefore continue to prioritize comprehensive metabolic and cardiovascular risk reduction while future research develops validated multimarker models and tissue-targeted interventions capable of restoring endothelial homeostasis.

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