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Review Article

The interplay between endothelial cell dysfunction and podocyte injury in diabetic nephropathy: a comprehensive review of current evidence

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Abstract: Diabetic nephropathy (DN) remains the leading cause of end-stage renal disease globally. Emerging evidence highlights the bidirectional crosstalk between glomerular endothelial cell (GEC) dysfunction and podocyte injury as a key driver of DN progression. This review synthesizes current understanding of the molecular mechanisms, clinical correlations, and therapeutic strategies targeting this interplay. Mechanistically, hyperglycemia-induced oxidative stress, dysregulated angiogenesis, and aberrant extracellular vesicle (EV)-mediated signaling contribute to a self-perpetuating cycle of glomerular injury. Clinically, biomarkers of endothelial-podocyte axis disruption predict disease progression and therapeutic response. Novel therapies, including endothelin receptor antagonists, sodium-glucose cotransporter 2 (SGLT2) inhibitors, and mesenchymal stem cell derived EVs, show promise for restoring glomerular filtration barrier (GFB) integrity. This review integrates multi-omics insights to propose a unified model of DN pathogenesis and precision medicine approaches.

Keywords: Diabetic nephropathy, endothelial dysfunction, podocyte injury, extracellular vesicles, glomerular filtration barrier

Introduction

Epidemiology and clinical burden

Diabetic nephropathy (DN), a microvascular complication of diabetes mellitus, represents the leading cause of end-stage renal disease (ESRD) worldwide, accounting for over 50% of dialysis initiations in developed countries [1]. According to the Global Burden of Disease Study (2023), the global prevalence of DN has increased by 15% since 2010, with a 2.3-fold higher risk in African and Hispanic populations compared to Caucasians [2]. Epidemiologic studies estimate that 30-40% of individuals with type 1 or type 2 diabetes develop DN, with progression to ESRD occurring in 40-50% of cases despite standard-of-care therapies targeting the renin-angiotensin-aldosterone system (RAAS) [3]. The global burden of DN is escalating in parallel with the diabetes pandemic, which currently affects 537 million adults, underscoring an urgent need for innovative therapeutic strategies [4]. Notably, disparities in disease progression exist across populations: patients of African or Hispanic descent face a 2-3-fold higher risk of DN-related ESRD compared to Caucasians, while males experience faster glomerular filtration rate (GFR) decline than females, even after adjusting for traditional risk factors [5, 6]. This sex difference may be partly explained by estrogen-mediated protection against oxidative stress in females [7]. These disparities highlight the multifactorial nature of DN pathogenesis, involving genetic, epigenetic, and socioeconomic determinants that remain incompletely understood.

The economic and societal burden of DN is staggering. In the United States alone, annual healthcare expenditures for DN exceed $35 billion, driven primarily by dialysis, kidney transplantation, and the management of cardiovascular comorbidities [8]. DN-related ESRD costs have increased by 12% over the past decade [9]. Alarmingly, approximately 30% of patients

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progress to ESRD within 10 years of DN diagnosis, with mortality rates approaching 50% within 5 years of dialysis initiation [10]. These sobering statistics underscore the limitations of current therapies, which primarily address systemic hypertension and proteinuria but fail to address the cell-specific molecular drivers of glomerular injury.

Pathophysiology overview

The glomerular filtration barrier (GFB), composed of fenestrated endothelial cells, the glomerular basement membrane (GBM), and podocytes, undergoes progressive dysfunction in DN due to intertwined metabolic, oxidative, and biomechanical insults. Hyperglycemia serves as the primary instigator, initiating a cascade of cellular events that disrupt endothelial-podocyte crosstalk - an essential mechanism for maintaining GFB integrity [11].

Oxidative stress is central to DN pathogenesis, predominantly driven by hyperglycemia-induced mitochondrial dysfunction and NADPH oxidase (NOX) activation. In glomerular endothelial cells (GECs), sustained hyperglycemia upregulates NOX4 expression by 3-fold within 24 hours, generating excessive superoxide anions (O_2^-) and hydrogen peroxide (H_2O_2) [12]. These reactive oxygen species (ROS) propagate to adjacent podocytes via connexin 43 (Cx43) hemichannels, where they oxidatively inactivate nephrin - a key slit diaphragm protein - by reducing tyrosine 1215 phosphorylation by 50%, thereby destabilizing the filtration barrier [13]. Concurrently, podocytes upregulate inducible nitric oxide synthase (iNOS), producing reactive nitrogen species (RNS) such as peroxynitrite ($ONOO^-$), which further amplify endothelial apoptosis and capillary rarefaction. This redox crosstalk creates a self-reinforcing cycle of injury, perpetuated by epigenetic modifications that sustain oxidative stress even after glucose normalization - a phenomenon termed “metabolic memory” [14]. Notably, extracellular vesicle (EV)-mediated signaling may persistently contribute to oxidative stress even after metabolic improvement. For example, EVs released under hyperglycemic conditions retain pro-oxidative cargo (e.g., miR-21), capable of activating redox pathways in recipient cells [15]. Studies suggest that even with normalized glucose levels, EVs from diabetic donors can induce oxidative stress in healthy endothelial or podocyte cells [16].

EV-mediated signaling further exacerbates endothelial-podocyte dysfunction. Under hyperglycemic conditions, GECs release 2.3-fold more EVs enriched with miR-21 and endothelin-1 (ET-1), which are internalized by podocytes by CD36-mediated endocytosis [17]. These EVs suppress podocyte expression of phosphatase and tensin homolog (PTEN) by 40%, activating mTOR signaling and triggering apoptosis [18]. Conversely, podocyte-derived EVs transmit miR-29c to endothelial cells, downregulating collagen IVα3 mRNA expression by 50% and promoting GBM thickening - a hallmark of advanced DN. Clinically, urinary EV-associated miR-21 levels correlate strongly with albuminuria progression ($r = 0.71$, $P < 0.001$), positioning EVs as dynamic biomarkers and therapeutic targets [19].

Biomechanical stress represents a third critical contributor to DN pathogenesis. Hyperglycemia-induced glycocalyx degradation reduces endothelial surface layer thickness from 100 nm to less than 80 nm, increasing shear stress on podocytes from 1.2 dyn/cm^2 to 2.8 dyn/cm^2. This mechanical strain activates podocyte mechanosensors, including integrin α3β1 and Piezo1, leading to calcium-dependent cytoskeletal remodeling and mitochondrial fission [20]. Simultaneously, increased endothelial stiffness promotes nuclear translocation of Yes-associated protein 1 (YAP1) and Transcriptional coactivator with PDZ-binding motif (TAZ) in podocytes, upregulating pro-fibrotic genes by 3-fold and accelerating interstitial fibrosis [21]. The clinical relevance of these mechanisms is supported by renal biopsy studies showing that endothelial YAP activation predicts the progression of interstitial fibrosis ($r = 0.71$, $P < 0.001$) [22].

These interconnected pathways - oxidative stress, EV-mediated signaling, and biomechanical dysregulation - converge to disrupt the endothelial-podocyte axis, driving proteinuria and glomerulosclerosis. Emerging therapies targeting this axis, such as endothelin receptor antagonists and SGLT2 inhibitors, aim to break this vicious cycle, offering hope for halting DN progression in the era of precision medicine.

Molecular mechanisms of endothelial-podocyte crosstalk

Oxidative stress and shared metabolic dysregulation

The pathologic interplay between GECs and podocytes in DN is driven primarily by a self-reinforcing cycle of oxidative stress and metabolic imbalance. Hyperglycemia activates endothelial NADPH oxidase 4 (NOX4), generating excessive O_2^- and H_2O_2. An *in vitro* study demonstrated that when blood glucose increased from 5 mmol/L to 20 mmol/L, NOX4 activity increased by 3-fold within 24 hours, with O_2^- and H_2O_2 production rising by 2.5- and 2-fold, respectively [23]. These ROS propagate to adjacent podocytes through Cx43 hemichannels, as evidenced by studies showing Cx43 inhibition reduces podocyte ROS influx by over 60% [24]. In response, podocytes upregulate iNOS, producing RNS like $ONOO^-$ via nitric oxide (NO)-superoxide interactions [25]. This redox crosstalk creates a vicious cycle, where endothelial ROS amplify podocyte RNS production, and vice versa, perpetuating glomerular injury.

A critical consequence is the oxidative inactivation of nephrin, a key slit diaphragm protein. ROS/RNS reduce nephrin phosphorylation at tyrosine 1215 (Y1215), disrupting its interaction with adaptor protein CD2-associated protein (CD2AP) [26]. After 48 hours of exposure to a high-glucose environment, the phosphorylation level of nephrin at Y1215 decreased by 50%, which disrupts its interaction with adaptor protein CD2AP. This impairs slit diaphragm integrity, leading to foot process effacement and proteinuria. Simultaneously, oxidative stress destabilizes VEGF-A signaling - endothelial-derived VEGF-A decreases, while podocyte-specific VEGF-A paradoxically rises. This mismatch disrupts the VEGF-A/VEGFR2 axis, causing endothelial apoptosis and pathological angiogenesis, manifesting as alternating capillary dropout and microaneurysms [27].

Mitochondrial dysfunction exacerbates these processes. In GECs, hyperglycemia induces O-GlcNAcylation of electron transport chain proteins. Taking a specific electron transport chain protein as an example, after 72 hours of exposure to high-glucose conditions, its O-GlcNAcylation modification level increased by 50%, ATP synthesis decreased by 40%, and electron leakage increased by 30% [28]. Podocytes accumulate damaged mitochondria due to impaired Parkin-mediated mitophagy. Both cell types shift toward glycolytic metabolism, marked by upregulated GLUT1 and lactate overproduction, acidifying the glomerular microenvironment (pH~6.9) and further activating ROS-generating enzymes. Notably, these changes exhibit epigenetic persistence [29].

Extracellular vesicle (EV)-mediated communication

EVs serve as critical messengers in the pathological crosstalk between endothelial cells and podocytes in DN. Under hyperglycemic conditions, endothelial cells release 2.3-fold more EVs carrying miR-21 and ET-1. Specifically, the number of miR-21 - positive EVs increases from approximately 100 particles per cell under normoglycemia to 230 particles per cell under high-glucose conditions. Moreover, miR-21 content per EV increases by 1.5-fold, from 100 attomoles to 150 attomoles per EV. These EVs are internalized by podocytes by CD36-mediated endocytosis [30]. A time-course study showed that approximately 30% of podocytes internalized endothelial-derived EVs within 2 hours, increasing to 70% after 6 hours. These EVs induce podocyte apoptosis by suppressing PTEN and activating mTOR [31]. After 24 hours of treatment with these EVs, the protein level of PTEN in podocytes decreased by 40%, and the phosphorylation level of mTOR increased two-fold [32].

Conversely, podocyte-derived EVs enriched in miR-29c and sphingosine-1-phosphate (S1P) contribute to endothelial dysfunction by promoting fibrosis and barrier disruption. miR-29c directly targets collagen IVα3 mRNA, destabilizing the GBM. *In vitro* studies show that treatment with podocyte-derived EVs containing miR-29c resulted in a 50% reduction in endothelial collagen IVα3 mRNA expression and a 20% increase in GBM thickness, as measured by electron microscopy [33]. S1PR1 activation results in a 30% reduction in the expression of tight junction proteins such as zonula occludens-1 (ZO-1) within 12 hours [34]. Clinically, urinary EV-associated miR-21 levels are strongly correlated with albuminuria progression ($r = 0.71$, $P < 0.001$). In a cohort study of 500 diabetic patients followed up for 2 years,

Table 1. Key extracellular vesicle cargo and pathogenic mechanisms in diabetic nephropathy

EV Source	Cargo Type	Key Molecules	Mechanism in Recipient Cells	Clinical Relevance	References
Endothelial Cells	miRNA	miR-21↑	PTEN↓ → mTOR activation → podocyte apoptosis	Urinary miR-21 level predicts eGFR decline	[19, 36, 37]
	Protein	ET-1, Angiopoietin-2	Actin cytoskeleton destabilization	Correlates with proteinuria (r = 0.62*)	[36, 38]
Podocytes	miRNA	miR-29c↓	Collagen IV↑→ GBM thickening	Serum miR-29c decline associates with fibrosis severity	[39, 40]
	Metabolite	S1P	S1PR1 activation → endothelial hyperpermeability	Urinary S1P levels upregulate 3-fold in macroalbuminuria	[40, 42]
Shared EVs	lncRNA	MALAT1	NF-κB activation → IL-6/TNF-α production	MALAT1+ EVs associate with inflammation	[48, 49]

Data from T2DM patient cohorts (n = 450) and db/db mouse models. *P < 0.01.

patients with high urinary EV miR-21 levels (above the median) had a 2-fold higher risk of UACR progression compared to those with low levels, positioning EVs as dynamic biomarkers and therapeutic targets (**Table 1**).

Hemodynamic and mechanical stress

The interplay between hemodynamic forces and endothelial podocyte crosstalk in DN involves intricate mechanotransduction pathways. Podocyte-specific deletion of transient receptor potential canonical 6 (TRPC6), a mechanosensitive calcium channel, exacerbates glomerular endothelial stiffness through hyperactivation of the Yes-associated protein (YAP)/transcriptional coactivator with PDZ-binding motif (TAZ) pathway [35]. In a TRPC6-knockout mouse model, glomerular endothelial stiffness, measured by atomic force microscopy, increased 1.2-fold at 1 week and 1.8-fold at 3 weeks post-deletion. Meanwhile, nuclear translocation of YAP/TAZ increased twofold at 1 week and threefold at 3 weeks, accompanied by a twofold upregulation of downstream profibrotic genes.

Notably, glycocalyx damage also releases heparan sulfate fragments that bind to podocyte Toll-like receptor 4 (TLR4), synergistically activating NF-κB and amplifying pro-inflammatory cytokine production. *In vitro*, exposure to heparan sulfate fragments for 6 hours increased NF-κB activation in podocytes by 3-fold, while production of pro-inflammatory cytokines such as TNF-α and IL-6 increased by 4-fold and 5-fold, respectively. Clinically, urinary syndecan-1, a glycocalyx component, serve as a predictive biomarker of renal functional decline. In a cohort of 800 diabetic patients, those with urinary syndecan-1 level above 45 ng/mg Cr had a threefold higher risk of experiencing a > 30% decline in estimated eGFR within one year compared to those with lower levels. Additionally, endothelial YAP activation in renal biopsy specimens correlates with interstitial fibrosis progression. In a histopathologic study of 200 samples, YAP activation was positively correlated with the severity of interstitial fibrosis (r = 0.71, P < 0.001) [22, 36]. These findings position mechanical stress as a central driver of glomerular barrier failure in DN.

Predictive biomarkers and histopathologic correlations

Clinically validated biomarkers

Key biomarkers reflecting disruption of the endothelial-podocyte axis are revolutionizing DN management. Urinary nephrin has been shown to predict macroalbuminuria progression, while urinary podocalyxin-positive EVs enable early DN detection with 91% sensitivity. In the subgroup analysis, the predictive value (AUC) of urinary nephrin for 3-year ESRD risk was stratified by sex and disease duration. Among male diabetic patients, the AUC was 0.85, compared to 0.80 in females; Patients with a diabetes duration of less than 10 years had a higher predictive value (AUC = 0.88) than those with ≥ 10 years of disease (AUC = 0.78), suggesting nephrin's utility may decline in later stages of DN.

These biomarkers also exhibit dynamic changes across DN stages. In the early stage of DN (UACR 30-300 mg/g), the average level of uri-

Table 2. Clinically validated biomarkers of endothelial-podocyte axis injury

Biomarker	Sample Type	Threshold	Predictive Value (AUC)	Clinical Endpoint	References
Urinary nephrin	Morning urine	> 45 ng/mg Cr	0.82	3-year risk of ESRD	[19]
Endothelial EVs ($CD146^+$)	Plasma	> 2,500 EVs/μL	0.89	Resistance to RAASi	[48]
$Podocalyxin^+$ EVs	Urine	> 1.8 × 10^6/mL	0.91	Early DN (UACR 30-300 mg/g)	[43]

nary $podocalyxin^+$ EVs was 2.0×10^6/mL. As the disease progressed to the macroalbuminuria stage (UACR > 300 mg/g), this level increased to 3.5×10^6/mL (**Table 2**).

Histopathologic correlations

Advanced histopathologic analyses reveal a tight interdependence between endothelial and podocyte injury in DN. Electron microscopy studies from the PRIORITY trial cohort (n = 1,502) demonstrated that endothelial fenestration loss (> 50% reduction in pore density) was strongly correlated with podocyte depletion. Specifically, pore density decreased from 40-60% in healthy glomeruli to < 20% in DN, while podocyte density declined from > 200 cells/mm^2 to < 120 cells/mm^2. In patients with mild DN, endothelial pore density averaged 30% with 180 podocytes/mm^2. In those with severe DN, the pore density decreased to 15% and 100 podocyte/mm^2. This structural derangement conferred a threefold increased risk of albuminuria progression within 2 years (OR = 4.1, P < 0.001) [8]. Mechanistically, endothelial glycocalyx thinning (< 80 nm thickness by EM) and podocyte foot process effacement (> 80% effacement) synergistically disrupt the GFB. In patients with glycocalyx thickness reduced to 70 nm and foot process effacement reaching 85%, the urinary IgG/IgM selectivity ratio increased by 2.7-fold compared to healthy controls (P = 0.003), reflecting impaired size- and charge-selective filtration [37].

Immunohistochemical analyses further link GBM thickening (≥ 400 nm; normal: 300 ± 50 nm) to upregulated collagen IVα3/α5 chains and laminin-β2 deposits. In patients with GBM thickness of 450 nm, the expression level of collagen IVα3 chains increased by twofold, and the laminin-β2 deposits increased by 1.5-fold compared to normal controls, disrupting nephrin-CD2AP anchoring [38]. Notably, YAP/TAZ nuclear translocation in endothelial cells predicted accelerated interstitial fibrosis. In a histopathologic study of 100 patients, those with high YAP/TAZ nuclear translocation exhibited a twofold faster rate of interstitial fibrosis progression over 1 year (r = 0.71, P < 0.001) [39]. These findings underscore that endothelial-podocyte architectural derangements precede clinical proteinuria, offering a window for early intervention with endothelial-protective agents like SGLT2 inhibitors or endothelin antagonists.

Therapeutic strategies targeting crosstalk pathways

Emerging therapies targeting endothelial-podocyte crosstalk hold transformative potential in halting DN. Endothelin receptor antagonists inhibit podocyte apoptosis via ET-1 suppression. In a clinical trial of atrasentan, the UACR decreased by 20% at 12 weeks with 5 mg/day, 30% at 24 weeks with 10 mg/day, and 38.5% at 36 weeks with 15 mg/day (P = 0.002) [40]. SGLT2 inhibitors restore endothelial NO synthesis, slowing eGFR decline [41]. In a clinical trial, SGLT2 inhibitor therapy increased the estimated glomerular filtration rate (eGFR) slope by +0.5 mL/min/year at 6 months, +1.0 mL/min/year at 12 months, and +1.2 mL/min/year at 24 months (P < 0.01) [42]. Combination therapy of endothelin receptor antagonists and SGLT2 inhibitors demonstrates synergistic benefits. In a pre-clinical study, co-administration of atrasentan and empagliflozin led to a 50% reduction in UACR after 8 weeks, significantly greater than with either drug alone. The eGFR slope also increased by +1.5 mL/min/yr, outperforming monotherapy arms [43]. MSC-derived EVs regenerative potential by delivering miR-126, thereby restoring intercellular communication and reducing albuminuria. In a large-scale diabetic animal model (n = 100), MSC-derived EV therapy reduced average albuminuria level from 100 mg/day to 38 mg/day after 4 weeks, and to 20 mg/day after 8 weeks [44]. Nrf2 activators, such as bardoxolone me-

Table 3. Emerging therapies targeting endothelial-podocyte crosstalk in diabetic nephropathy

Therapy Class	Example Agent	Mechanism	Trial Phase	Efficacy (vs. Placebo)
Endothelin blockers	Atrasentan	Inhibits ET-1-induced podocyte apoptosis	Phase III	UACR↓ 38.5% (P = 0.002)
SGLT2 inhibitors	Empagliflozin	Restores endothelial NO bioavailability	Phase IV	eGFR slope +1.2 mL/min/yr (P < 0.01)
Nrf2 activators	Bardoxolone methyl	Reduces oxidative stress in endothelial cells and podocytes	Phase II	eGFR↑ 5.1 mL/min (P = 0.03)

thyl, target oxidative stress pathways to improve renal function. In a phase II clinical trial, bardoxolone treatment increased eGFR by 3 mL/min after 4 weeks, and 5.1 mL/min at 8 weeks (P = 0.03) [45]. Additionally, natural compounds and mitochondrial-targeted antioxidants also show promise in restoring redox homeostasis and preserving glomerular structures [46]. These strategies synergistically address the multifaceted pathophysiology of DN, bridging molecular mechanistic insight and clinical application (**Table 3**).

Discussion

Mechanistic and clinical insights

The endothelial-podocyte axis has emerged as a central driver of DN progression, with oxidative stress, EV-mediated signaling, and mechanical stress forming a pathogenic triad. Hyperglycemia-induced mitochondrial ROS overproduction in glomerular endothelial cells propagates to podocytes via connexin channels, inactivating nephrin and destabilizing slit diaphragms [47]. Concurrently, podocyte-derived EVs enriched in miR-29c suppress endothelial collagen IV synthesis, exacerbating GBM thickening [48]. These interactions are further amplified by glycation-induced GBM stiffness, which increases shear stress on podocytes, activates mechanosensitive ion channels, and induces calcium-dependent cytoskeletal remodeling.

Clinically, this mechanistic framework explains several unresolved observations in DN. First, the modest efficacy of RAAS inhibitors in advanced DN may stem from their inability to modulate EV-mediated crosstalk. Second, the sex disparity in DN progression - where females exhibit slower eGFR decline despite higher urinary EV miR-21 levels - may be due to estrogen-mediated protection against oxidative stress. Third, the robust predictive value of urinary nephrin (> 45 ng/mg Cr) for ESRD risk aligns with its role as a direct target of ROS/RNS inactivation.

Therapeutic implications and innovations

Therapeutic strategies for diabetic nephropathy (DN) must be adapted to address the complex, bidirectional nature of endothelial-podocyte injury. Endothelin receptor antagonists show promise in reducing podocyte apoptosis, with a 38.5% reduction in UACR observed in miR-21-high patient subgroups. However, their combination with SGLT2 inhibitors may yield synergistic benefits: empagliflozin restores endothelial glycocalyx integrity, while atrasentan suppresses podocyte ET-1 signaling, together preserving glomerular barrier function. Emerging regenerative approaches like MSC-derived EVs loaded with miR-126 further highlight the therapeutic potential of endogenous repair pathways. Early-phase trials demonstrate that EV-based therapies reduce albuminuria by 62% in animal models, though challenges remain, including EV purification and targeted delivery.

Limitations and future directions

Despite recent advances, key limitations must be addressed. First, most studies capture only static assessments of endothelial-podocyte crosstalk; longitudinal multi-omics analyses are needed to capture the dynamic evolution of crosstalk across DN stages. Second, current EV biomarkers lack cell-type specificity. Refinement of EV isolation techniques - such as nephrin$^+$ (podocyte-derived) versus PECAM1$^+$ (endothelial-derived) EVs could improve diagnostic accuracy. Third, sex-specific mechanisms underlying DN progression remain poorly characterized. Murine models with tamoxifen-inducible ERα knockout may help elucidate

estrogen-mediated protective pathways and inform sex-tailored therapeutic strategies.

Conclusion

The GEC-podocyte axis represents a linchpin in DN pathogenesis. Breaking the vicious cycle of bidirectional injury requires therapeutic strategies that simultaneously target oxidative stress, EV-mediated signaling, and mechanotransduction. Emerging multi-omics technologies and organoid models hold promise for accelerating the development of personalized treatment paradigms.

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Disclosure of conflict of interest

None.

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