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ENDOTHELIAL DYSFUNCTION IN AUTOIMMUNE GLOMERULAR DISEASES: PATHOGENESIS AND EARLY DIAGNOSIS

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Abstract: Endothelial dysfunction plays a crucial role in the pathogenesis of autoimmune glomerular diseases. This thesis analyzes the structural and functional characteristics of glomerular endothelial cells and the mechanisms of their injury in autoimmune conditions. Immune complex deposition and anti-endothelial antibodies in lupus nephritis, neutrophil adhesion to endothelium in ANCA-associated vasculitis, and mesangial-endothelial interactions in IgA nephropathy are considered as primary causes of endothelial dysfunction. Complement dysregulation, oxidative stress, and cytokine effects are evaluated as common pathogenetic factors enhancing endothelial injury. The significance of early diagnostic markers of endothelial dysfunction, particularly von Willebrand factor, thrombomodulin, endothelin-1, and extracellular vesicles in blood and urine, is highlighted. Special attention is paid to the sensitivity of urinary endothelial markers in detecting local intrarenal endothelial damage and their prognostic value in the development of tubulointerstitial fibrosis. The thesis discusses the possibilities of early diagnosis and prediction of disease progression based on endothelial dysfunction markers, as well as the prospects of endothelium-targeted therapeutic strategies.

Keywords: endothelial dysfunction, glomerular diseases, autoimmune pathology, von Willebrand factor, thrombomodulin, endothelin-1, early diagnosis,

Introduction: The glomerular endothelium, with its unique fenestrated structure and rich glycocalyx, represents a critical interface between the circulating blood and the renal filtration apparatus. Far from being a passive barrier, glomerular endothelial cells (GEnCs) actively participate in the regulation of vascular tone, coagulation balance, immune cell trafficking, and permselectivity through intricate crosstalk with neighbouring podocytes and mesangial cells. In autoimmune glomerular diseases, this finely tuned endothelial homeostasis is disrupted, leading to a state of endothelial dysfunction that contributes significantly to disease initiation and progression. Understanding the mechanisms of endothelial injury in these conditions and identifying early markers of endothelial activation has become increasingly important for timely diagnosis and therapeutic intervention.

Endothelial dysfunction in autoimmune glomerular diseases arises through multiple convergent pathways, each reflecting the underlying autoimmune process. In lupus nephritis, immune complex deposition along the glomerular capillary wall triggers a cascade of endothelial responses, including increased expression of adhesion molecules, enhanced secretion of pro-inflammatory cytokines (IL-6, IL-8, TNF- α), and activation of complement pathways. The type I interferon signature characteristic of systemic lupus erythematosus renders endothelial cells particularly susceptible to apoptosis and creates an imbalance between regulatory and activating factors. Furthermore, the development of specific anti-endothelial cell antibodies directly contributes to vascular injury.

In ANCA-associated vasculitis, a distinct mechanism operates wherein neutrophils activated by anti-neutrophil cytoplasmic antibodies adhere to the endothelium, releasing toxic granules, reactive oxygen species, and neutrophil extracellular traps that cause direct endothelial injury and fibrinoid necrosis. The alternative complement pathway, particularly C5a-mediated amplification of inflammation, perpetuates endothelial dysfunction. Similarly, in IgA

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nephropathy, the deposition of IgA1 in the mesangium initiates local inflammation that extends to the endothelium through mesangium-endothelium interactions, with high-affinity binding of IgA1 to glomerular endothelial cells promoting cytokine production, glycocalyx loss, and barrier dysfunction. Complement activation via the lectin pathway and deficiencies in regulatory factors further exacerbate endothelial damage.

Emerging evidence highlights the importance of endothelial-podocyte crosstalk in maintaining the filtration barrier. Vascular endothelial growth factor (VEGF) produced by podocytes is essential for endothelial health, and disruption of this signalling axis—whether through podocyte injury in focal segmental glomerulosclerosis or direct effects on VEGF receptors in diabetic kidney disease—results in endothelial dysfunction and impaired angiogenesis. The endothelin system also plays a significant role, with increased endothelin-1 expression observed in sclerotic forms of glomerulonephritis, particularly when accompanied by arterial hypertension. This vasoactive peptide induces endothelial oxidative stress and contributes to the progression of renal fibrosis.

Beyond disease-specific mechanisms, shared molecular pathways amplify endothelial injury across different autoimmune glomerular diseases. Complement dysregulation, whether through classical pathway activation in immune complex-mediated diseases or alternative pathway abnormalities in C3 glomerulopathy, directly injures the glomerular endothelium. The coagulation cascade becomes activated as a consequence of endothelial damage, favouring local microangiopathy and further compromising the glomerular microcirculation. Systemic inflammation, driven by effector cytokines such as IFN- γ , TNF- α , and IL-17 from infiltrating T cells, macrophages, and NK cells, promotes endothelial dysfunction through induction of reactive oxygen species-producing enzymes like NADPH oxidases and loss of nitric oxide bioavailability. This creates a self-perpetuating cycle of inflammation, oxidative stress, and vascular injury that drives disease progression.

The recognition that endothelial dysfunction precedes clinically overt renal damage has stimulated intensive investigation into circulating and urinary biomarkers that reflect endothelial activation and injury. Traditional markers such as von Willebrand factor (VWF), thrombomodulin (TM), and endothelin-1 have been extensively studied in various forms of glomerulonephritis. Notably, while serum concentrations of TM and VWF in patients with chronic glomerulonephritis may remain within the normal range—suggesting absence of widespread systemic endothelial injury—their urinary concentrations significantly exceed control values. This dissociation indicates that endothelial damage in glomerular diseases may be compartmentalised to the renal microvasculature, and urinary markers may offer greater sensitivity for detecting local intrarenal endothelial dysfunction.

Urinary VWF, plasminogen activator inhibitor-1 (PAI-1), and fibrin degradation products correlate with disease activity and severity in chronic glomerulonephritis, with particularly elevated levels in progressive forms accompanied by nephrotic syndrome and renal failure. Importantly, these markers also reflect the development of tubulointerstitial fibrosis, a key determinant of long-term renal outcomes. Patients with morphologically verified tubulointerstitial involvement (interstitial area exceeding 20%) demonstrate higher urinary excretion of endothelial dysfunction markers compared to those without fibrosis. The combination of elevated VWF and reduced urinary VEGF—indicating both endothelial injury and impaired regenerative capacity—appears especially characteristic of progressive disease.

More recently, extracellular vesicles (EVs) released from activated or injured endothelial cells have emerged as promising biomarkers. These microparticles, detectable in both circulating blood and urine, carry surface markers reflecting their cellular origin and cargo molecules that mediate intercellular communication. In autoimmune diseases affecting the kidney, including lupus nephritis and ANCA-associated vasculitis, circulating and urinary EVs have been implicated in disease pathogenesis and show potential as early indicators of renal involvement. Endothelial-derived EVs can transfer bioactive molecules to recipient cells, modulating

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inflammation, coagulation, and angiogenesis, and may represent not only biomarkers but also active participants in disease propagation.

The persistence of endothelial dysfunction during clinical remission, regardless of the morphological form of glomerulonephritis, suggests that endothelial injury contributes not only to acute disease manifestations but also to chronic progression. Endothelial activation promotes a prothrombotic state and drives sclerotic changes through stimulation of cellular proliferation and extracellular matrix accumulation. The identification of endothelial dysfunction markers with prognostic value, particularly endothelin-1 in hypertensive patients and urinary VWF/PAI-1 in those with tubulointerstitial fibrosis, offers opportunities for risk stratification and monitoring of disease progression.

From a therapeutic perspective, recognising the central role of endothelial dysfunction opens avenues for targeted interventions. Antiplatelet agents, angiotensin-converting enzyme inhibitors, and agents that stabilise the endothelial glycocalyx or restore nitric oxide bioavailability may complement conventional immunosuppressive therapy. The development of criteria for prescribing such agents based on endothelial marker profiles could enable more personalised treatment approaches.

Conclusion: Endothelial dysfunction represents a fundamental pathophysiological mechanism in autoimmune glomerular diseases, arising from disease-specific immune insults and converging on common pathways of inflammation, complement activation, and oxidative stress. The recognition that glomerular endothelial injury often precedes podocyte damage and overt proteinuria positions endothelial dysfunction as both an early event in disease pathogenesis and a potential therapeutic target. Urinary markers, particularly VWF, TM, and PAI-1, offer accessible tools for detecting intrarenal endothelial involvement and monitoring disease activity and fibrotic progression. Emerging biomarkers such as extracellular vesicles may provide even greater sensitivity and mechanistic insight. As our understanding of glomerular endothelial biology advances, integrating endothelial assessment into routine clinical evaluation could enhance early diagnosis, improve prognostic accuracy, and guide targeted interventions in patients with autoimmune glomerular diseases.