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Review Article

Endothelial dysfunction in chronic kidney disease: Mechanisms, biomarkers, diagnostics, and therapeutic strategies

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Abstract

Endothelial cells regulate vascular tone, blood flow, coagulation, and inflammation, with heterogeneous populations serving specific roles throughout the body. In the kidney, endothelial cells maintain vascular integrity and function, contribute to filtration, and support other renal structures. Nitric oxide (NO) is a key signaling molecule that maintains vascular tone and endothelial function. It is synthesized by nitric oxide synthase (NOS) isoforms, with endothelial NOS playing a central role in vascular health. Chronic kidney disease (CKD) is characterized by reduced NO bioavailability, driven by the accumulation of endogenous NOS inhibitors such as asymmetric dimethylarginine (ADMA) and symmetric dimethylarginine (SDMA). Uremic toxins, oxidative stress, and proinflammatory cytokines contribute to a prothrombotic and proinflammatory state, contributing to endothelial dysfunction and exacerbating cardiovascular (CV) risks in CKD. Biomarkers such as ADMA, SDMA, endothelial microparticles, and soluble adhesion molecules offer insights into vascular health, while invasive or noninvasive diagnostic techniques can assess endothelial function in CKD. Effective management strategies focus on enhancing NO bioavailability, controlling oxidative stress, reducing inflammation, and optimizing dialysis to minimize uremic toxin levels. Emerging therapeutic approaches, including antioxidant therapies and endothelial progenitor cell-based interventions, show promise in preserving vascular function. A multifaceted approach to managing endothelial dysfunction is critical for mitigating CV complications and improving patient outcomes in CKD.

Keywords: *Chronic kidney disease, Diagnostic techniques, Endothelial dysfunction, Endothelium, Therapeutic approaches*

Introduction

The endothelium, a monolayer of cells lining blood vessels, plays a crucial role in vascular homeostasis by regulating vascular tone, platelet activity, leukocyte adhesion, and angiogenesis [1]. It produces various vasoactive substances, including nitric oxide (NO), prostanoids, and endothelin, which modulate vascular function [2]. Endothelial dysfunction, characterized by reduced NO bioavailability and a proinflammatory phenotype, contributes to atherosclerosis and cardiovascular diseases (CVDs) [1]. Risk factors such as hypertension, diabetes, heart failure, and chronic kidney disease (CKD) can impair endothelial function, leading to vasoconstriction, platelet activation, and vascular inflammation [2,3].

Endothelial dysfunction is a critical factor in the increased cardiovascular (CV) risk associated with CKD [4]. Patients with CKD have a high risk of developing CVD, even in the early stages of CKD [5]. CV risk in patients with CKD is elevated due to both traditional factors – such as smoking, dyslipidemia, diabetes, and hypertension – and CKD-specific mechanisms, including the accumulation of uremic toxins, persistent inflammation, oxidative stress, and vascular dysfunction [5,6]. Targeting endothelial dysfunction may benefit various CKD stages, making it an ideal therapeutic focus for treating and preventing renal disease [4].

This review explores the role of the nitric oxide synthase (NOS) pathway and its inhibitors in CKD, focusing on how endothelial dysfunction contributes to CV complications. Furthermore, it highlights endothelial health biomarkers, current endothelial function assessment methods, and potential therapeutic approaches to protect vascular integrity. This work

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aims to provide insights into novel strategies for managing CV risk and improving patient outcomes by addressing the interplay between endothelial dysfunction and CKD.

The nitric oxide synthase pathway

NO is a crucial signaling molecule involved in various physiological processes, essential for maintaining endothelial function and vascular tone in the CV system [7]. It is synthesized by three isoforms of NOS: neuronal NOS (nNOS), inducible NOS, and endothelial NOS (eNOS) [8]. In blood vessels, eNOS produces NO from L-arginine, requiring cofactors such as nicotinamide adenine dinucleotide phosphate, flavin adenine dinucleotide, flavin mononucleotide, and tetrahydrobiopterin [8]. The activity of eNOS is regulated by various factors, including calcium ions, phosphorylation, and shear stress, exerted by blood flow. In blood vessels, NO diffuses from endothelial cells into adjacent smooth muscle cells, where it activates soluble guanylyl cyclase (sGC), an enzyme that catalyzes the conversion of guanosine triphosphate to cyclic guanosine monophosphate, leading to smooth muscle relaxation and vasodilation [9]. It also inhibits platelet aggregation and leukocyte adhesion, maintaining vascular homeostasis [7] [Figure 1]. Dysfunction in NO production or bioavailability characterizes endothelial dysfunction associated with CV diseases such as hypertension, atherosclerosis, and heart failure [9,10].

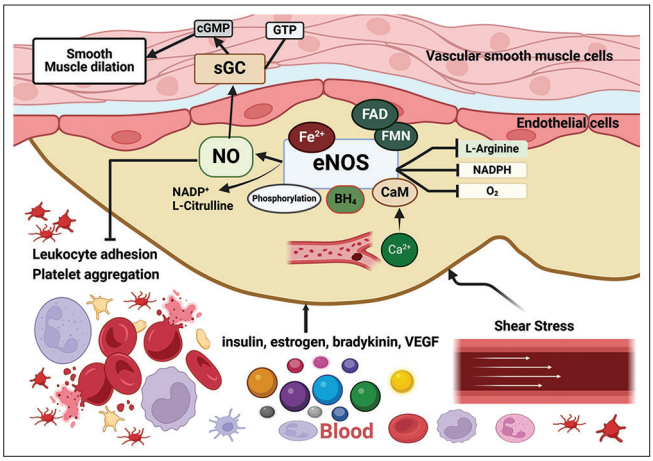

Figure 1: The nitric oxide (NO) generation through endothelial nitric oxide synthase (eNOS) coupling. NO is an essential signaling molecule in the cardiovascular system, playing a key role in maintaining endothelial health and regulating blood vessel tone. eNOS in blood vessels produces NO from L-arginine with the help of cofactors such as nicotinamide adenine dinucleotide phosphate, flavin adenine dinucleotide, flavin mononucleotide, and tetrahydrobiopterin. NO production in endothelial cells is mainly regulated through eNOS activation and is influenced by several factors, such as calcium ions, phosphorylation, shear stress, hormones, and growth factors (insulin, estrogen, bradykinin, and vascular endothelial growth factor), oxygen availability, L-arginine and cofactors. Once produced, NO diffuses from endothelial cells into nearby smooth muscle cells, activating soluble guanylyl cyclase. This activation transforms guanosine triphosphate into cyclic guanosine monophosphate, resulting in smooth muscle relaxation and vasodilation. NO also prevents platelet aggregation and leukocyte adhesion, supporting overall vascular stability and function. NADPH: Nicotinamide adenine dinucleotide phosphate, FAD: Flavin adenine dinucleotide, FMN: Flavin mononucleotide, BH_4: Tetrahydrobiopterin, VEGF: Vascular endothelial growth factor, NO: Nitric oxide, GTP: Guanosine triphosphate, sGC: Soluble guanylyl cyclase, eNOS: Endothelial nitric oxide synthase, cGMP: Cyclic guanosine monophosphate, CaM: Calmodulin. Created in BioRender.com

Endogenous inhibitors of nitric oxide synthase in chronic kidney disease

CKD is characterized by impaired endothelial function, primarily due to reduced NO bioavailability. One of the significant contributors to this dysfunction is the presence of endogenous inhibitors of NOS, the enzyme responsible for NO production. These inhibitors interfere with the normal synthesis of NO, exacerbating vascular dysfunction, inflammation, and increased CV risks associated with CKD.

Asymmetric dimethylarginine (ADMA) is an endogenous inhibitor of NOS that plays a crucial role in CV and renal diseases. ADMA competitively inhibits NOS, reducing NO production and contributing to endothelial dysfunction [2]. In CKD, ADMA accumulates due to impaired renal excretion, leading to increased CV risk and accelerated disease progression [11]. ADMA has emerged as an independent predictor of CV events and CKD progression [12].

Symmetric dimethylarginine (SDMA) is a structural isomer of ADMA that competes with L-arginine for cellular uptake, indirectly affecting NO synthesis [13]. While SDMA does not directly inhibit NOS, it can reduce endothelial NO production and increase reactive oxygen species (ROS) in endothelial cells [14]. In CKD, SDMA levels are elevated due to reduced renal clearance, contributing to endothelial dysfunction and CV complications [13]. SDMA has been shown to suppress vascular endothelial growth factor-induced eNOS phosphorylation and cause NOS uncoupling in glomerular endothelial cells, leading to increased oxidative stress [15]. In addition, SDMA has emerged as a valuable marker for detecting the early stages of CKD and assessing CV risk [14]. These findings suggest that SDMA is not an inert metabolite but plays a significant role in vascular dysfunction in CKD.

Dimethylarginine dimethylaminohydrolase (DDAH) is crucial in regulating ADMA levels and inhibiting NO production. Two DDAH isoforms exist: DDAH-1 predominates in the kidney and liver, while DDAH-2 is found mainly in the vasculature [16]. Both isoforms increase eNO production through different mechanisms: DDAH-1 acts in an ADMA-dependent manner, while DDAH-2 operates independently of ADMA [17]. DDAH activity is often reduced in CV and renal diseases, leading to ADMA accumulation and endothelial dysfunction [18]. Impaired DDAH function creates a vicious cycle where increased ADMA levels further reduce NO availability, contributing to disease progression. Recent studies suggest that DDAH may regulate endothelial function through ADMA-dependent and independent mechanisms, highlighting its potential as a therapeutic target in CV and renal diseases [17].

ADMA and SDMA are uremic toxins accumulating in CKD and inhibiting NOS [13]. Both strongly predict CV events and mortality in CKD patients and the general population [19]. ADMA is metabolized by DDAH [16]. Elevated levels of ADMA and SDMA contribute to endothelial dysfunction, inflammation, and atherosclerosis [20]. The uremic milieu in CKD impairs DDAH activity and promotes oxidative stress, exacerbating endothelial dysfunction [13]. While progress has

been made in animal studies in ADMA-lowering therapies, further research is needed to develop specific treatments for human diseases related to elevated ADMA and SDMA levels [19]. Table 1 shows the summary of endogenous NOS inhibitors in CKD.

ADMA and SDMA are primarily formed endogenously through the methylation of protein-bound L-arginine by protein arginine methyltransferases (PRMTs). Type I PRMTs catalyze the formation of ADMA through asymmetric dimethylation of protein-bound monomethylarginine, while Type II PRMTs generate SDMA through symmetric dimethylation of the same substrate. Both ADMA and SDMA are liberated during protein degradation, and although an exogenous dietary contribution has been suggested, its significance remains unclear. ADMA metabolism predominantly occurs through DDAH enzymes (DDAH1 and DDAH2), which convert ADMA into citrulline and dimethylamine, with a smaller contribution from alanine–glyoxylate aminotransferase 2 (AGXT2) through conversion to α-keto-δ-(N, N-dimethylguanidino) valeric acid (DMGV). Butylation and methylation pathways play a minor role in ADMA clearance, while renal excretion is secondary. In contrast, SDMA relies almost entirely on renal excretion for elimination, as it is not a substrate for DDAH. Its metabolism, although limited, involves AGXT2 as the primary enzyme, contributing to the formation of DMGV, with minimal involvement of butylation and methylation pathways. These differences in metabolism highlight ADMA's role in interfering with NO synthesis and endothelial function, while SDMA primarily reflects renal clearance efficiency, making it a strong marker of renal function [13]. The elimination of SDMA and ADMA is not solely reliant on renal clearance. The liver also plays a significant role in metabolizing and removing these molecules, contributing importantly to their overall elimination from the body [13].

Endothelium dysfunction in chronic kidney disease

In CKD, the endothelium is exposed to multiple stressors, including uremic toxins, oxidative stress, and proinflammatory cytokines, contributing to a prothrombotic and proinflammatory state, leading to reduced NO production and increased NO breakdown, exacerbating vascular dysfunction, and promoting CV complications [21,22]. Nontraditional risk factors, such as decreased soluble α-Klotho and Vitamin D levels, increased fibroblast growth factor-23 and phosphate and accumulation of uremic toxins, exacerbate endothelial abnormalities in CKD [23]. These factors activate various cellular signaling pathways, including ROS, mitogen-activated protein kinase/nuclear factor-κB (MAPK/NF-κB), aryl hydrocarbon receptor, and receptor for advanced glycation end products pathways, leading to increased inflammation, oxidative stress, leukocyte adhesion, and cell death in endothelial cells, further impair endothelial function in CKD [21,22]. In advanced stages of CKD, endothelial cells may undergo a process known as endothelial-to-mesenchymal transition, where they lose their endothelial markers and acquire mesenchymal characteristics, contributing to fibrosis. This transition is driven by inflammatory cytokines such as transforming growth factor-beta and is associated with the progression of renal fibrosis and systemic vascular damage [24]. Understanding these mechanisms is crucial for developing targeted interventions to mitigate CV complications in CKD patients [Figure 2].

The gut microbiota plays a critical role in regulating endothelial function through its metabolites and inflammatory pathways. Microbial-derived compounds such as short-chain fatty acids (SCFAs), trimethylamine (TMA), trimethylamine N-oxide (TMAO), uremic toxins, and structural components such as lipopolysaccharides and peptidoglycan, along with gaseous molecules such as hydrogen sulfide, NO, carbon monoxide, and methane, can cross the intestinal epithelium and influence the vascular system [25,26]. These effects occur through two primary mechanisms: stimulation of the enteric nervous system, which activates brain centers controlling CV function, and direct entry into the bloodstream through the blood–intestinal barrier, where they modulate tissue and organ function to maintain circulatory homeostasis. Dysbiosis, or an imbalance in gut microbial composition, exacerbates vascular diseases by increasing inflammatory markers, compromising gut barrier integrity, and promoting systemic inflammation, ultimately contributing to endothelial dysfunction through both direct and indirect pathways [25,26].

Biomarkers of endothelial function in chronic kidney disease

Endothelial dysfunction is a crucial feature of CKD and is closely linked to the progression of the disease and the development of CV complications. Biomarkers that reflect endothelial health and dysfunction can provide valuable insights into vascular function in CKD patients. These

Table 1: Summary of endogenous nitric oxide synthase inhibitors in chronic kidney disease

Inhibitor/factor	Mechanism	Effect in CKD
ADMA	Inhibits eNOS by competing with L-arginine, reducing NO synthesis	Increased ADMA due to impaired renal clearance, leading to endothelial dysfunction, oxidative stress, and hypertension
SDMA	Reduces L-arginine transport into cells, indirectly reducing NO synthesis	Elevated SDMA levels due to reduced renal clearance, contribute to endothelial dysfunction
DDAH	Breaks down ADMA, reducing its inhibitory effect on NO production	Reduced DDAH activity leads to accumulation of ADMA, worsening endothelial dysfunction
Uremic toxins	Impaired NO synthesis due to accumulation of ADMA, SDMA, and other uremic toxins	Uremic toxins exacerbate endothelial dysfunction and CV damage

ADMA: Asymmetric dimethylarginine, SDMA: Symmetric dimethylarginine, DDAH: Dimethylarginine dimethylaminohydrolase, CKD: Chronic kidney disease, eNOS: Endothelial nitric oxide synthase, NO: Nitric oxide, CV: Cardiovascular

biomarkers are beneficial for identifying endothelial injury, monitoring disease progression, and evaluating the efficacy of therapeutic interventions. Table 2 is a summary of the key biomarkers with clinical evidence for predictive value in CKD. However, further interventional studies are essential to comprehensively evaluate the relationship between these biomarkers of endothelial dysfunction and CKD.

ADMA and SDMA are endogenous amino acids that play crucial roles in endothelial dysfunction and CV disease, particularly in CKD [13]. ADMA and SDMA accumulate in CKD due to reduced renal clearance, leading to endothelial dysfunction and increased CV risk [13].

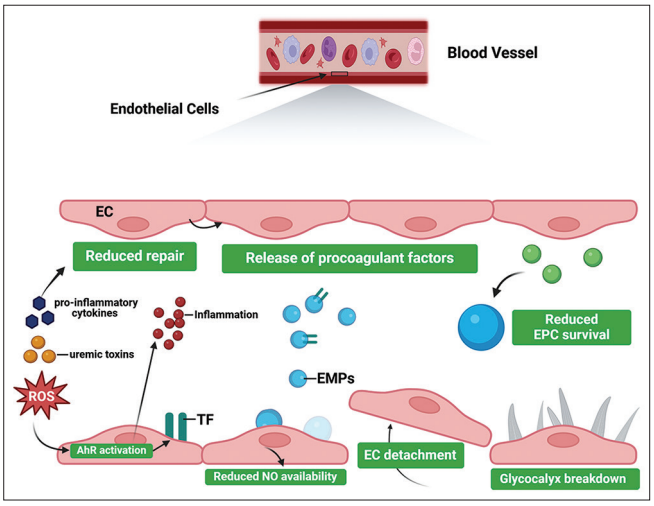

Figure 2: Endothelium dysfunction in chronic kidney disease (CKD). CKD contributes to endothelial dysfunction by causing the buildup of uremic toxins, oxidative stress, and proinflammatory cytokines, which lead to oxidative stress in endothelial cells (ECs). This creates a procoagulant environment, marked by increased tissue factor expression and procoagulant endothelial microparticle release. CKD also reduces the availability of nitric oxide, damages the glycocalyx – a protective layer on ECs – and weakens the repair ability of both mature ECs and endothelial progenitor cells. AhR: Aryl hydrocarbon receptor, ROS: Reactive oxygen species, EMP: Endothelial microparticles, TF: Tissue factor, EPC: Endothelial progenitor cell. Created in BioRender.com

Endothelial microparticles (EMPs) are vesicles released from activated or apoptotic endothelial cells, as markers of endothelial dysfunction [27]. They play crucial roles in coagulation, inflammation, and angiogenesis, contributing to vascular disease progression [27]. In CKD, EMPs are associated with uremic toxins and inflammatory biomarkers, potentially contributing to atherosclerosis development [28].

Soluble adhesion molecules such as soluble intercellular adhesion molecule-1 (sICAM-1) and soluble vascular cell adhesion molecule-1 (sVCAM-1) are markers of endothelial activation and inflammation [29]. These molecules are elevated in end-stage renal disease patients and are independent predictors of all-cause and CV mortality [30]. In predialysis patients, elevated levels of sICAM-1 and sVCAM-1 are associated with malnutrition, inflammation, and CVD [31].

Von Willebrand factor (vWF) is a glycoprotein that plays a crucial role in hemostasis and is a marker of endothelial dysfunction in various CV disorders [32]. Chen *et al*. noted that patients with CKD had significantly higher levels of multiple biomarkers, including ADMA, L-arginine, sVCAM-1, sE-selectin, and vWF, compared to controls of endothelial dysfunction measured by flow-mediated dilation (FMD) and nitroglycerin-induced dilation [33].

MicroRNAs are small noncoding RNAs that regulate gene expression posttranscriptionally, influencing various endothelial functions such as barrier integrity, vascular tone, angiogenesis, and leukocyte trafficking, and play a crucial role in endothelial dysfunction associated with CKD [34]. For example, microRNA-92a is upregulated in CKD patients and animal models, contributing to endothelial dysfunction by suppressing key protective molecules [35]. Conversely, microRNA-142-3p is downregulated in CKD, and its restoration improves vascular relaxation in uremic mice [36]. MicroRNA-145 and microRNA-155 significantly reduced in CKD patients compared to controls [37]. MicroRNA-145 and microRNA-155 are positively associated with FMD and negatively associated with ADMA

Table 2: Summary of the biomarkers of endothelial function with clinical evidence for predictive value in chronic kidney disease

Biomarkers	Clinical evidence	Predictive value
ADMA	Elevated in CKD due to reduced renal clearance; inhibits NO synthesis, leading to endothelial dysfunction and increased CV risk	A strong predictor of CV morbidity and mortality in CKD, especially in advanced stages
SDMA	It reflects renal function, is elevated in CKD due to impaired clearance, and contributes to endothelial dysfunction indirectly	Reliable marker for renal function and CV complications in CKD
EMPs	Released from apoptotic/activated ECs; linked to uremic toxins, coagulation, inflammation, and angiogenesis	Correlates with vascular damage, atherosclerosis, and CV complications in CKD
Soluble adhesion molecules (sICAM-1 and sVCAM-1)	Elevated in CKD, especially ESRD, are markers of inflammation and endothelial activation and are associated with malnutrition and CV risk	Independent predictors of all-cause and CV mortality in CKD patients
vWF	Elevated in CKD, a marker of endothelial injury, correlates with other markers such as sVCAM-1 and ADMA, involved in hemostasis and vascular pathology	Predictive of CV events and mortality in CKD patients
MicroRNAs	Dysregulated in CKD; microRNA-92a upregulated, promoting dysfunction; microRNA-142-3p, -145, and -155 downregulated, with links to improved vascular function	Emerging biomarkers for endothelial health and molecular pathways of vascular complications in CKD

ADMA: Asymmetric dimethylarginine, SDMA: Symmetric dimethylarginine, EMPs: Endothelial microparticles, vWF: Von Willebrand factor, CKD: Chronic kidney disease, CV: Cardiovascular, sICAM-1: Soluble intercellular adhesion molecule-1, sVCAM-1: Soluble vascular cell adhesion molecule-1, ESRD: End-stage renal disease, NO: Nitric oxide, ECs: Endothelial cells

in a cross-sectional study of 60 patients with CKD and 60 controls [37].

Our study group also collectively explores the associations between various biomarkers and endothelial function measured by a digital thermal monitoring (DTM) test of vascular reactivity index (VRI) in patients with CKD and those undergoing hemodialysis. Serum indoxyl sulfate, galectin-3, and adiponectin negatively impacted endothelial function in patients with CKD [38-40]. In addition, adipocyte fatty acid-binding protein and angiopoietin-like protein 3 levels were associated with endothelial dysfunction in hemodialysis patients [41,42]. Further interventional studies are needed to examine the relationship between multiple endothelial dysfunction biomarkers and CKD.

Methods of assessment of endothelial function

Assessing endothelial function is critical for understanding vascular health, especially in the context of CV diseases, CKD, diabetes, and other conditions that impair endothelial performance. Several methods are available to evaluate endothelial function, ranging from noninvasive techniques to more invasive procedures, each with varying degrees of complexity and accuracy. Table 3 shows the summary of comparing the methods of assessing endothelial function with advantages, limitations, and clinical applicability in CKD.

FMD is a noninvasive method for assessing endothelial function, which plays a crucial role in CV health [43,44]. The technique measures vasodilation in response to increased blood flow and shear stress, primarily mediated by NO release [44]. FMD has been shown to be affected by CV risk factors and related to structural arterial disease and CV outcomes, validating its use in studying arterial disease pathophysiology [45]. While widely adopted, there is considerable variability in FMD protocols, analysis methods, and result interpretation across studies. Standardized protocols and analysis software have improved the method's reproducibility, enabling its use in population studies and multicenter settings [43,45]. However, following strict guidelines to ensure accurate and comparable results is crucial, as methodological differences can significantly impact response magnitude and data interpretation [43].

Reactive hyperemia-peripheral arterial tonometry (RH-PAT) is a noninvasive technique for assessing endothelial function by measuring changes in pulse wave amplitude in response to reactive hyperemia [46]. The reactive hyperemia index (RHI) derived from RH-PAT has been associated with CV risk and adverse events [47]. RH-PAT offers advantages over other methods, such as FMD, due to its user-friendly and automated nature [48]. However, RH-PAT results can be influenced by factors such as digital artery stenosis, which may lead to an underestimation of RHI [46]. The technique has shown promise in predicting late CV events, with a lower RHI associated with higher adverse event rates during follow-up [47]. Despite its potential, further research is needed to address methodological and clinical aspects before widespread application [46].

DTM is a noninvasive method for assessing endothelial function by measuring fingertip temperature changes during reactive hyperemia [49]. The DTM technique measures the temperature rebound in the fingertips following a period of ischemia (blood flow occlusion) induced by a blood pressure cuff on the upper arm. When the cuff is deflated, blood rushes back into the arm and hand, generating shear stress on the endothelial cells lining the blood vessels. The endothelium, if healthy, responds by releasing NO and other vasodilatory substances, increasing blood flow to the extremities. The extent of the temperature change in the fingertips serves as an indirect indicator of the vasodilatory capacity of the microcirculation and, by extension, endothelial function and is measured as VRI [50,51]. Studies have shown that DTM can effectively identify individuals with coronary heart disease and increased CV risk [52]. DTM indices correlate with traditional risk factors, subclinical atherosclerosis, and myocardial perfusion defects, providing incremental predictive value over risk factor assessment alone [49]. These findings suggest that DTM is a promising tool for early CV risk assessment and monitoring treatment responses in clinical settings [50,51].

Laser Doppler flowmetry (LDF) is a noninvasive technique for measuring microvascular blood perfusion [53]. It uses laser light to detect the movement of red blood cells in the outermost layer of tissue, typically up to 1 mm deep [53]. While LDF is a well-established method for assessing microvascular endothelial function, it has limitations that can affect signal interpretation, including processing bandwidth, motion artifacts, and probe pressure [53]. The technique can be combined with iontophoresis of vasoactive substances such as acetylcholine (ACh) to evaluate endothelial function in various pathological conditions [54]. LDF has been applied to study blood flow in human skin, revealing rhythmical variations and day-to-day fluctuations in skin blood flow [53]. Despite its versatility, standardization of protocols is needed to reduce controversies in the literature and improve understanding of CVD progression [54].

Coronary angiography with ACh infusion is an invasive technique to assess coronary artery endothelial function [55]. In healthy vessels, ACh stimulates NO release, causing vasodilation, while in dysfunctional endothelium, it may paradoxically induce vasoconstriction [56]. This method has revealed that coronary risk factors are associated with impaired endothelium-dependent vasodilation, suggesting it may be an early marker of atherosclerosis [55]. While considered the gold standard for detecting endothelial dysfunction, the procedure carries some risks. Adverse reactions occur in about 16% of patients, including rare but serious events such as occlusive spasms, with younger patients (under 60) being at higher risk [57]. Despite these risks, intracoronary ACh infusion remains valuable for evaluating endothelial function, particularly in complex cases or research settings [56].

The cold pressor test (CPT) is a method used to assess CV reactivity and endothelial function by immersing a subject's hand in cold water [58]. This triggers a sympathetic

Table 3: Summary of comparisons of the methods of assessing endothelial function

Method	Invasiveness	What is measured	Procedure	Significance	Advantages	Limitations	Clinical applicability in CKD
FMD	Noninvasive	Arterial dilation	Ultrasound measures artery diameter after blood flow occlusion	Reduced dilation indicates endothelial dysfunction	Gold standard for NO-dependent vasodilation Directly assesses conduit artery function	Operator-dependent Time-consuming Expensive equipment Affected by confounders	Research focused on endothelial dysfunction in CKD Provides insights into CV risk
RH-PAT	Noninvasive	Pulse wave amplitude	The finger probe measures pulse wave amplitude after occlusion	Lower pulse wave amplitude indicates endothelial dysfunction	Noninvasive, automated, and reproducible Comprehensive endothelial function index	Indirect measurement Influenced by skin thickness or vascular compliance High cost	Suitable for large-scale studies or outpatient use Useful for CV risk stratification in CKD
PAT	Noninvasive	Pulse wave amplitude	The finger probe measures pulse wave amplitude after occlusion	Lower pulse wave amplitude suggests endothelial dysfunction	Noninvasive, standardized, and easy to perform	Indirect measure May miss systemic endothelial dysfunction	Useful for assessing microvascular dysfunction in CKD A surrogate marker for CV risk
DTM	Noninvasive	Temperature rebound	Temperature of fingertips measured after occlusion	Reduced temperature rebound reflects impaired endothelial function	Noninvasive and cost-effective Easy to perform in outpatient settings	Indirect and affected by ambient factors Validation is limited compared to FMD or PAT	Potential screening tool for endothelial dysfunction in CKD Needs further research for reliability
Laser Doppler flowmetry	Noninvasive	Blood flow	Laser measures changes in blood flow in response to stimuli	Useful for assessing microvascular endothelial function	High sensitivity for microvascular blood flow Real-time assessment of skin circulation	Requires specialized equipment and expertise Limited clinical standardization	Research focused on microvascular dysfunction in CKD Complements other vascular assessments
Coronary angiography with ACh	Invasive	Coronary artery dilation	Acetylcholine induces vasodilation in coronary arteries	Direct assessment of coronary endothelial function	Direct measure of coronary endothelial function Evaluate macro- and microvascular dysfunction	Invasive and risky Requires specialized facilities	Rarely used in CKD due to invasiveness Applied in advanced coronary dysfunction cases
Cold pressor test	Noninvasive	Blood pressure and vascular tone	Hand immersed in cold water; measures blood pressure response	Heightened blood pressure response indicates endothelial dysfunction	Simple and inexpensive Evaluate vascular reactivity through sympathetic response	High variability and indirect measure Affected by systemic factors	Provides insights into vascular and autonomic dysfunction in CKD Best used with other methods

CKD: Chronic kidney disease, NO: Nitric oxide, FMD: Flow-mediated dilation, RH-PAT: Reactive hyperemia peripheral arterial tonometry, PAT: Peripheral arterial tonometry, DTM: Digital thermal monitoring, ACh: Acetylcholine, CV: Cardiovascular

nervous system response, leading to increased heart rate, blood pressure, and myocardial oxygen demand [58]. The CPT causes a significant increase in blood pressure and pulse in all subjects, with some studies showing differences in NO levels between groups [59]. The test involves the release of various neurohormones, including norepinephrine, endothelins, prostaglandins, and angiotensin II [60]. Not all antihypertensive drugs block the exaggerated pressor response induced by cold stress, with α- and β-blockers being the most effective [60]. Despite ongoing debates about its predictive value for hypertension, the CPT remains a valuable tool for assessing CV reactivity.

To effectively integrate endothelial function tests into CKD care, noninvasive methods such as RH-PAT, PAT, and DTM are recommended for early detection of vascular dysfunction and routine follow-ups, particularly in high-risk or rapidly progressing CKD cases. A comprehensive vascular assessment can be achieved by combining macrovascular evaluation techniques such as FMD or RH-PAT with microvascular-focused methods such as DTM or LDF. These tests also offer value in monitoring the effectiveness of therapeutic interventions, including renin–angiotensin system inhibitors, statins, and lifestyle modifications. Advanced techniques, such as FMD, LDF, and coronary angiography with ACh, should be reserved for research or specialized nephrology clinics to study complex cases of endothelial dysfunction. For routine care, practical and cost-effective options such as DTM and PAT provide an accessible means to improve vascular health assessment while balancing clinical utility and resource constraints.

Endothelial dysfunction impact on cardiovascular disease in chronic kidney disease

Endothelial dysfunction is a critical factor in the development of CVD in CKD patients. It is characterized by reduced NO bioavailability, which is nearly universal in advanced CKD [21]. Multiple mechanisms contribute to endothelial dysfunction in CKD, including inflammation, oxidative stress, and uremic toxins [21,22]. These factors promote atherosclerosis, vascular calcification, and hypertension, leading to increased CV risk [61]. Traditional risk factors alone cannot explain the high prevalence of CVD in CKD, emphasizing the importance of nontraditional factors such as endothelial dysfunction [21]. Management of CKD patients should focus on preventing and treating CV complications through targeted interventions addressing endothelial dysfunction [21].

Protecting endothelial health in chronic kidney disease

Preserving endothelial health is, therefore, a key target in managing CKD and mitigating its systemic complications. Protecting the endothelium in CKD involves addressing factors that impair endothelial function, such as oxidative stress, inflammation, NO deficiency, and uremic toxin accumulation, as well as employing therapeutic interventions that promote endothelial repair and stability.

Oxidative stress and inflammation play central roles in this process, with reduced NO bioavailability being a hallmark of CKD [21]. Protecting endothelial health in CKD requires strategies to reduce oxidative stress and inflammation. Antioxidant therapies, such as N-acetylcysteine (NAC), have shown promise in attenuating oxidative stress induced by uremic serum in both *in vitro* and *in vivo* studies [62]. Using an *in vitro* model, flavonoids (apigenin, genistein, and quercetin) and synthetic antioxidant enzyme mimetics (ebselen, EUK-134, and EUK-118) enhancing glutathione peroxidase pathways, particularly ebselen and NAC, effectively mitigated ROS production, reduced inflammatory markers such as ICAM-1 expression, and inhibited the activation of p38MAPK and NF-κB signaling pathways in endothelial cells exposed to uremic conditions [63]. These approaches and other antioxidants and anti-inflammatory agents may help restore proper endothelial function and reduce CV risk in CKD patients [21].

CKD patients exhibit lower NO levels and higher ADMA concentrations, a potent inhibitor of eNOS [13]. Therapeutic approaches to enhance NO bioavailability include L-arginine or L-citrulline supplementation, as L-arginine availability is reduced in CKD due to impaired renal biosynthesis [64]. Statins have shown promise in improving endothelial function in patients with hypercholesterolemia and atherosclerosis [65]. Other potential strategies involve antioxidant vitamins, tetrahydrobiopterin supplementation, and natural plant extracts rich in phytochemicals [65]. Lowering ADMA concentrations and enhancing DDAH activity are also being investigated as therapeutic targets [64].

Uremic toxins induce endothelial dysfunction in CKD through various mechanisms, such as damaging the endothelial monolayer structure and increasing permeability, overexpression of proinflammatory and prothrombotic proteins, and formation of EMPs [66]. Managing uremic toxin levels is crucial for preserving endothelial health in CKD, and potential therapeutic strategies include improving dialysis techniques and using phosphate binders to control serum phosphate levels [67].

CKD is characterized by persistent inflammation, which contributes to endothelial dysfunction and CV complications [68]. Endothelial cells become activated in response to inflammatory cytokines, oxidative stress, and uremic toxins, leading to increased expression of adhesion molecules and leukocyte recruitment [69,70]. Therapeutic approaches targeting inflammation in CKD include addressing the source of inflammation, promoting healthy lifestyle changes, and using pharmacological interventions with pleiotropic effects [68]. In addition, novel targeted anticytokine therapies are being investigated to mitigate the effects of chronic inflammation on endothelial health in CKD patients [70].

In addition to protecting the endothelium from damage, strategies that promote endothelial repair and regeneration are also important for maintaining endothelial health in CKD. Endothelial progenitor cells (EPCs) play a key role in repairing damaged endothelium and maintaining vascular integrity [71]. EPCs from bone marrow or tissue-resident sources contribute to endothelial regeneration through direct engraftment and paracrine effects [71,72]. In CKD, uremia and inflammation are associated with reduced EPC counts, potentially contributing to increased CV risks [73]. EPC-based therapies have shown promise in various models of CV and kidney diseases [73]. In diabetic kidney disease, EPCs exhibit regenerative capabilities by repairing endothelial damage, reducing oxidative stress, and modulating inflammatory responses in preclinical studies [74]. However, challenges in EPC research include the lack of standardized definitions and methodologies [72].

Hypertension is a common complication in CKD, contributing to disease progression and CV risk [73,75]. The pathophysiology of hypertension in CKD is complex, involving factors such as reduced nephron mass, sodium retention, sympathetic nervous system overactivity, and endothelial dysfunction [73]. Management strategies include dietary salt restriction and pharmacological interventions [73,75]. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are recommended first-line treatments, particularly for CKD patients with proteinuria [75]. Other antihypertensive agents may be necessary for optimal blood pressure control, such as diuretics, beta-blockers, and calcium channel blockers [75]. While specific blood pressure targets remain debated, achieving adequate control is crucial for slowing CKD progression and reducing CV risk [73,75].

Sodium–glucose cotransporter-2 inhibitors (SGLT-2 inhibitors) or mineralocorticoid receptor antagonists (MRAs) can improve endothelial function through mechanisms such as

reduced oxidative stress, inflammation, and vascular stiffness while enhancing NO bioavailability [76]. In a systematic review and meta-analysis study with a total of 26 clinical studies (668 participants), SGLT-2 inhibitors significantly improve endothelial function, as measured by FMD [77]. Steroidal MRAs, such as spironolactone and eplerenone, effectively reduce endothelial dysfunction but are limited in advanced CKD [78]. Finerenone, a nonsteroidal MRA upregulation of manganese superoxide dismutase, reduces superoxide anion levels and enhances NO bioavailability, contributing to improved endothelial function [79].

Nonpharmacological approaches, including plant-dominant low-protein diets, extra-virgin olive oil consumption, adapted physical activity, and ketoanalogues further enhance endothelial health by addressing gut dysbiosis, oxidative stress, and metabolic disorders [76].

Protecting endothelial health in CKD requires a multifaceted approach that addresses the underlying causes of endothelial dysfunction. Therapeutic strategies aimed at enhancing NO bioavailability, reducing oxidative damage, promoting endothelial repair, and managing CV risk factors can help preserve endothelial function and reduce the progression of CKD and its associated complications. However, despite the promising potential of therapies targeting endothelial health in CKD, several barriers hinder their implementation in clinical practice. High costs and limited accessibility, particularly for advanced treatments such as anticytokine therapies and EPC-based therapies, pose significant challenges, especially in resource-limited settings. Nonpharmacological approaches, including plant-dominant low-protein diets and adapted physical activity, are often hindered by poor patient adherence, cultural preferences, and the lack of structured support systems. Furthermore, many interventions lack robust clinical evidence from large-scale randomized controlled trials, limiting their integration into standard care. Safety concerns, such as hyperkalemia with MRAs and potential unintended consequences of ADMA-lowering therapies, further complicate their use. Logistical and regulatory hurdles, including stringent approval processes and the need for specialized facilities or expertise, delay the adoption of novel therapies such as EPC-based and targeted anticytokine treatments. The multifactorial nature of CKD, involving oxidative stress, inflammation, uremic toxins, and vascular stiffness, adds complexity to therapeutic approaches, requiring combinations of treatments that increase care complexity. Addressing these barriers through enhanced cost management, feasibility improvements, strengthened clinical evidence, and educational campaigns is essential for translating these therapies into practical strategies to protect endothelial health and improve outcomes for CKD patients.

Conclusion

Endothelial dysfunction is a key driver of both CKD progression and the increased CV risk associated with the disease. Understanding the mechanisms behind endothelial dysfunction, including reduced NO bioavailability, increased oxidative stress, and chronic inflammation, provides a foundation for developing therapeutic strategies aimed at improving vascular health in CKD patients. Effective management of endothelial dysfunction has the potential to not only slow the progression of CKD but also reduce the risk of CV complications, ultimately improving the quality of life and survival of CKD patients.

Future research on endothelial function in CKD should expand beyond well-established pathways, such as ADMA and SDMA, to explore emerging and underexplored areas. Investigating the gut-vascular axis, including the role of gut microbiota-derived metabolites such as TMAO, phenylacetic acid, and SCFAs, could provide insights into systemic inflammation and vascular health. The regulatory roles of microRNAs and epigenetic modifications also hold potential as novel biomarkers and therapeutic targets for CKD-related endothelial dysfunction. Further studies on oxidative stress pathways, immune modulation, and endothelial repair mechanisms, such as those involving EPCs, could pave the way for innovative treatments. The development and evaluation of advanced therapies, including nonsteroidal MRA (e.g., finerenone), SGLT-2 inhibitors, and plant-based bioactive compounds, warrant further investigation. Nonpharmacological approaches, such as plant-dominant diets and interventions targeting gut dysbiosis, should also be explored for their impact on endothelial health. Integrating precision medicine and systems biology approaches and conducting longitudinal studies will be crucial for understanding the long-term effects of endothelial-targeted interventions on CV and renal outcomes in CKD.

Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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Conflicts of interest

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