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Differential Levels and Biological Roles of eNOS and SCUBE1 in Endothelial Dysfunction: A Systematic Review

Muhammad Abi Ghoffari Siregar[1,2], Hirowati Ali[3*], Rizki Rahmadian[4], Salsabila Faiha Wiendra Rasya[2]

[1]Master's Program in Biomedical Sciences, Faculty of Medicine, Universitas Andalas, Indonesia;
[2]Medical Clinical Student at RSUP Dr. M. Djamil, Padang, Faculty of Medicine, Universitas Andalas, Indonesia;
[3]Department of Biochemistry, Faculty of Medicine, Universitas Andalas, Indonesia;
[4]Department of Surgery, Faculty of Medicine, Universitas Andalas/ Dr. M. Djamil General Hospital, Padang, Indonesia;

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*Corresponding Author:
Hirowati Ali, Department of Biochemistry, Faculty of Medicine, Universitas Andalas, Kec. Pauh, 25175, Padang, Indonesia.
E-mail: hirowatiali@med.unand.ac.id

Abstract: Endothelial dysfunction (ED) is a systemic disorder marked by impaired nitric oxide (NO) availability, which is essential for maintaining vascular tone and managing oxidative stress. This dysfunction contributes to vascular pathologies such as atherosclerosis and coronary artery disease (CAD) by fostering vasoconstriction, increased permeability, and inflammatory responses, thereby highlighting the urgent need for biomarkers and interventions aimed at mitigating endothelial dysfunction and its associated risks. The relationship between eNOS and SCUBE1 relates to endothelial function and oxidative stress. This study seeks to clarify the benefits and drawbacks of each biomarker in its capacity as a preventive strategy against endothelial dysfunction. This systematic review, adhering to the PRISMA Checklist, examines evidence on the role of endothelial function and oxidative stress in endothelial dysfunction, with emphasis on the biomarkers eNOS and SCUBE1. Literature searches were conducted in PubMed, ScienceDirect, and Google Scholar, and study quality was appraised based on reported biomarker values and relevance. There were 8 articles with increased eNOS and decreased ROS in several treatments, associated with prevention of endothelial dysfunction. There were 6 articles with increased SCUBE1 in several diseases (breast cancer, STEMI, hashimoto's thyroiditis, peripheral ischemic, pulmonary arterial hypertension, atherosclerosis) being markers of endothelial dysfunction. Both biomarkers can work well according to their release pathways, they can be novel biomarkers of endothelial dysfunction in various diseases. Their main role is on endothelial function, SCUBE1 controls BMPR2 signaling (angiogenic, proliferation, apoptosis) and eNOS focuses on endothelial health through NO production (vasodilation, maintaining vascular tone).

Keywords: Biomarker, endothelial dysfunction, nitric oxide, platelet.

Introduction

Endothelial dysfunction (ED) is a systemic condition defined by an imbalance in endothelial mediator production – notably a reduction in nitric oxide (NO) bioavailability – leading to impaired vasodilation, pro-thrombotic tendency, and inflammation (Penna & Pagliaro, 2025). Epidemiologically, the prevalence of coronary endothelial dysfunction reaches 65-90% in patients with chest pain and non-obstructive coronary artery disease, with 50-70% demonstrating endothelium-dependent vascular dysfunction (Bockus & Kim, 2022). Functionally, ED manifests as increased vasoconstriction, vascular permeability, thrombosis, and leukocyte adhesion, which collectively promote atherogenesis and cardiovascular diseases like atherosclerosis and coronary artery disease (CAD).

ED often arises from multifactorial etiologies, including classic risk factors (e.g. hypertension, diabetes, dyslipidemia, smoking) that incite chronic endothelial injury. These risk factors trigger a pro-inflammatory endothelial phenotype: excess cytokine and chemokine release and upregulation of cellular adhesion molecules (CAMs), fostering leukocyte infiltration into the vessel wall. Given the central role of ED as an early, reversible precursor of vascular disease, there is intense interest in identifying biomarkers and interventions to detect and restore endothelial function (Li et al., 2022; Penna & Pagliaro, 2025).

The pathophysiology of endothelial dysfunction involves a central role of reactive oxygen species (ROS) and oxidative stress in creating an imbalance between ROS generation and antioxidant defense systems. Endothelial nitric oxide synthase (eNOS) plays a crucial role in vascular homeostasis through NO synthesis that regulates vascular tone, prevents platelet aggregation, and maintains endothelial cell integrity. Under normal conditions, eNOS efficiently produces NO, however, when structurally uncoupled, the enzyme shifts from generating NO to producing superoxide, exacerbating vascular oxidative damage. Excess ROS not only deactivate NO but also trigger harmful pathological pathways including NADPH oxidase activation, peroxynitrite formation, and endothelin overexpression (Janaszak-Jasiecka et al., 2023; Tran et al., 2022).

eNOS uncoupling occurs when electrons within the reductase domain, instead of reducing L-arginine to produce NO, are transferred to molecular oxygen forming superoxide. This phenomenon is more detrimental than simple eNOS inhibition because it converts a vasoprotective enzyme into a pro-oxidant source. Factors contributing to eNOS uncoupling include tetrahydrobiopterin (BH4) depletion, asymmetric dimethylarginine (ADMA) inhibition, and pathological post-translational modifications including S-glutathionylation. SCUBE1 (Signal Peptide, CUB Domain, and EGF-like Domain Containing 1), although predominantly platelet-associated, can enter circulation and accumulate in thrombus and atherosclerotic plaques. SCUBE1 release during endothelial dysfunction is triggered by thrombin activity, platelet activation, inflammation, and oxidative stress, linking it indirectly to endothelial pathology (Janaszak-Jasiecka et al., 2023; Łuczak et al., 2020).

The problem is an inverse pattern in endothelial dysfunction: SCUBE1 rises with platelet–endothelial activation and injury, whereas eNOS declines or uncouples, reducing nitric-oxide and raising oxidative stress. SCUBE1, a platelet–endothelial glycoprotein elevates in hypertension. Reduced eNOS boosts superoxide. Their negative correlation marks two facets of one process: SCUBE1 indexing platelet–endothelial activation and microvascular injury, and eNOS indicating vasoprotective capacity and longer-term homeostasis (Janaszak-Jasiecka et al., 2023; Łuczak et al., 2020).

This review synthesizes evidence on differential levels and roles of eNOS versus SCUBE1 in endothelial dysfunction. eNOS/NO is protective, yet measurement relies on surrogates, FMD and nitrite/nitrate, limited by NO's short half-life and systemic confounding (Daiber et al., 2019; Penna & Pagliaro, 2025). SCUBE1 is a circulating marker released from platelets during thrombin-driven activation; it localizes to thrombi and fosters adhesion and aggregation (Lin et al., 2023). Conceptually, eNOS loss signals diminished protection, whereas SCUBE1 gain signals thrombo-inflammation. Combining NO surrogates or FMD with SCUBE1 may improve early detection and risk stratification, but causal interplay, temporal dynamics, assay harmonization, and incremental prognostic value need prospective validation (Daiber et al., 2019; Lin et al., 2023).

Material and Methods

This systematic review has been executed following the guidelines by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Page et al., 2021).

Search strategy and study selection

This systematic review search strategy is to the PRISMA guideline, which uses three search engine databases, ScienceDirect, PubMed, Google Scholar (within 10 years years), with keywords: (endothelial dysfunction) AND (biomarker) AND (protein)

AND (platelet), this search was conducted by the researchers of this systematic review. Not only that, the use of the PICO strategy was used to guide researchers to find keywords related to the research study. The PICO systematic review includes

1. Population (P) leads to all patients who experience endothelial dysfunction;
2. Intervention (I) targeted to patients tested for e-NOS;
3. Comparison (C) targeted to patients tested for SCUBE1;
4. Outcome (O) comparing the effectiveness of e-NOS and SCUBE in patients with endothelial dysfunction

Inclusion and Exclusion Criteria

Screening for article eligibility was conducted using a search engine database, and inclusion criteria were selected according to the needs of this systematic review. Articles and studies that fit the criteria were selected as follows:

1. Articles using English and Indonesian language, not limited to Scopus-indexed journals, and applicable to nationally indexed journals from 2015-2024.
2. Additional keywords "e-NOS" or "eNOS" and "SCUBE1".
3. Original articles on assessing diagnostic value in endothelial dysfunction.
4. The search engine databases used were Google Scholar, PubMed, and ScienceDirect.
5. Free Full-text articles

In order to fulfill the inclusion criteria, it is imperative to establish exclusion criteria. In this regard, the following exclusion criteria are congruent with the systematic approach employed in this review:

1. Articles solely comprised of abstracts
2. Studies that do not align with the investigation of eNOS or e-NOS and SCUBE1
3. Replication of articles
4. Articles containing inadequate data

Data Extraction and Assessment of Study Quality

The articles in the databases were selected based on their titles and keywords. After this initial selection, the complete articles were thoroughly reviewed to confirm their adherence to the predetermined inclusion criteria. Data collection and organization were carried out using custom-designed tables to present the essential information effectively. Table 1 provides a comprehensive overview of the selected articles, including author(s), year of publication, methodology employed, resulting diagnosis value, and reference. The analysis of Table 1 includes authors, year of publication, study context, diagnosis value using the eNOS. Table 2 presents similar results that concern the SCUBE1 value, which represents the maximum observed percentage. A diagram illustrating the article selection process is presented in Figure 1, following the PRISMA flow format.

Study Outcomes

The primary outcome is to compare the effectiveness of e-NOS and SCUBE in patients with endothelial dysfunction.

Results and Discussion

Following PRISMA 2020, the flow diagram for this review depicts identification across three databases (PubMed, ScienceDirect, and Google Scholar) restricted to a 10-year window (2015–2024) and screened using predefined PICOS criteria (population: endothelial dysfunction; intervention/comparator: eNOS vs. SCUBE1; outcome: biomarker effectiveness), with English/Indonesian and free full-text as eligibility constraints; after deduplication, title/abstract screening, and full-text assessment that excluded non-original reports (e.g., reviews/case reports), non-target biomarkers, duplicate/republished items, and studies with inadequate data, the final synthesis comprised 8 eNOS-focused studies (generally showing increased eNOS activity/NO bioavailability with reduced ROS) and 6 SCUBE1-focused studies (reporting elevated SCUBE1 across several disease contexts), with box-level counts and exclusion reasons displayed at each stage in the diagram to ensure transparency and reproducibility.

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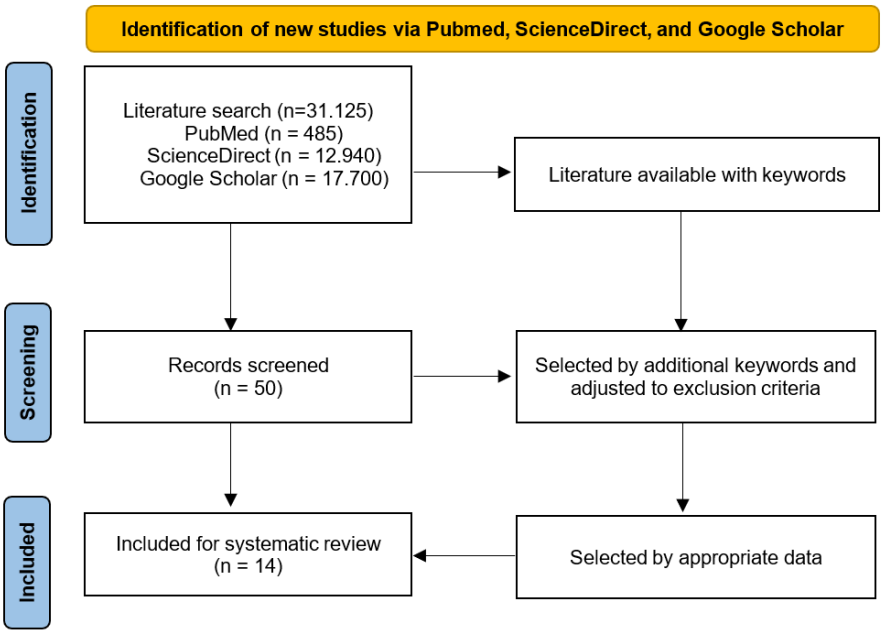

Figure 1. Flow Chart of Study Selection (PRISMA)

Table 1. Measurement of eNOS

Model/Context	Biological Function and value	References
Metabolic-syndrome rats; irbesartan	Biological function: Preserves eNOS coupling via BH4; raises NO; limits superoxide. Value:↑eNOS coupling (dimer/monomer ratio),↑NO bioavailability,↓superoxide,↑acetylcholine-induced vasorelaxation,↑BH4 availability	(Lamas et al., 2015)
Obese KKAy mice; olmesartan (AT1R block)	Biological function: AT1R blockade enhances eNOS Ser1177 phosphorylation and NO; lowers ROS. Value:↑Endothelium-dependent vasodilation,↑eNOS phosphorylation (Ser1177),↑NO levels,↓ROS production (aortic tissue and DHE staining)	(Takahashi et al., 2015)
HFD-obese rats; hesperetin	Biological function: Upregulates eNOS/NO and suppresses inflammatory cytokines in HFD-obesity. Value: ↑eNOS expression,↑NO production,↓TNF-α & IL-6,↓HOMA-IR, improved lipid profile	(Chakraborty & Ain, 2017)
ApoE−/− mice; metformin	Biological function: Activates PGC-1α → ↑eNOS expression/activity and NO; ↓oxidative stress. Value: ↑ PGC-1α, ↑ eNOS mRNA/protein, ↑ NO levels, ↑ ACh-induced vasodilation, ↓ ROS (via DHE staining)	(S. Xu et al., 2017)
OVX rats; estradiol/GPER	Biological function: Estradiol/GPER signaling boosts eNOS Ser1177 phosphorylation and NO. Value:↑eNOS phosphorylation and NO production with estradiol, GPER agonist (G1), enhanced acetylcholine-induced vasorelaxation in OVX rats	(Fredette et al., 2020)
HFD-obese mice;	Biological function: Ang-(1–7) activates eNOS/NO and suppresses	(Zhan et al.,

Ang-(1–7)	NOX2/NOX4-derived ROS. Value: ↑ eNOS phosphorylation,↑ NO bioavailability,↓ ROS production,↑ vasorelaxation,↓ NOX2/NOX4 expression	2020)
Mouse vascular dysfunction	Biological function: IL-4–PPARγ axis (eosinophils) promotes eNOS activation and NO. Value: ↑ eNOS phosphorylation (Ser1177),↑ NO levels,↑ PPARγ, improved vasodilation in wild-type mice; effects diminished in eosinophil-deficient or IL-4 knockout mice	(Stamm et al., 2021)
HUVECs; ox-LDL ± LPAR5 silencing	Biological function: ox-LDL via LPAR5/NLRP3 depresses eNOS/NO; LPAR5 silencing restores them and reduces oxidative stress. Value: ↓eNOS,↓NO with ox-LDL; reversed by LPAR5 knockdown. ↑CD31,↓α-SMA	(L. Xu et al., 2021)

SCUBE1 behaves as a context-dependent thrombo-inflammatory marker: it is elevated in prothrombotic/inflammatory or ischemia–reperfusion states including breast cancer, hypothyroidism, STEMI (especially with no-reflow), and experimental reperfusion consistent with platelet-endothelial activation and microvascular dysfunction; conversely, in PAH, lower plasma SCUBE1 associates with BMPR2-linked endothelial dysfunction, underscoring disease-specific directionality and the need for standardized matrices and cut-offs for risk stratification.

Table 2. Measurement of SCUBE1

Model/Context	Biological Function and value	References
Breast cancer vs control	Biological function: Platelet-endothelial activation marker; elevated in prothrombotic cancer milieu. Value: Higher serum SCUBE1 in breast cancer (2.36 ± 2.04 vs 0.153 ± 0.21 ng/mL) supports thrombo-inflammatory/endo-activation status.	(Topcu et al., 2015)
Hashimoto hypothyroidism	Biological function: Reflects endothelial injury and platelet activation in autoimmune hypothyroidism. Value: SCUBE1 and sCD40L significantly increased ($p < 0.05$)	(Bilir et al., 2016)
STEMI ± no-reflow	Biological function: Tracks thrombus/microvascular obstruction in STEMI (no-reflow). Value: SCUBE1 is highest in no-reflow (97.2 ± 8.9 ng/mL) vs STEMI w/o NR and controls—prognostic for microvascular dysfunction.	(Bolayır et al., 2017)
Limb ischemia–reperfusion (rat)	Biological function: Rises on reperfusion after ischemia—marker of endothelial stress recovery/platelet activation. Value: Increased in reperfusion vs ischemia/control ($p < 0.05$)	(Sogut et al., 2017)
Pulmonary arterial hypertension	Biological function: Links to BMPR2 pathway and pulmonary endothelial integrity in PAH. Value: Lower plasma SCUBE1 (< 5.46 ng/mL) discriminates PAH (OR 7.6; specificity 0.87)—diagnostic stratifier.	(Sun et al., 2020)
Psoriasis (subclinical atherosclerosis)	Biological function: Reflects vascular injury/angiogenic imbalance in inflammatory atherosclerosis risk. Value: Higher SCUBE1 (4.47 ± 2.40 ng/mL) in psoriasis aligns with subclinical atherosclerosis signaling.	(Ayvaz Çelik et al., 2023)

Discussion

Relation between eNOS, SCUBE1 and endothelial dysfunction

Endothelial nitric oxide synthase (eNOS) is an enzyme primarily expressed in endothelial cells, responsible for producing nitric oxide (NO), a crucial vasodilator and signaling molecule. NO plays a vital role in maintaining vascular tone by promoting the relaxation of smooth muscle cells in blood vessels, inhibiting platelet aggregation, and reducing inflammation (Tran et al., 2022). In a healthy endothelium, eNOS activity is tightly regulated to ensure the continuous release of NO, thus preserving vascular homeostasis. However, endothelial dysfunction is characterized by a reduction in NO bioavailability, resulting in impaired

vasodilation. This condition often serves as a precursor to various cardiovascular diseases, including atherosclerosis, hypertension, and diabetes-related complications. The underlying mechanisms leading to endothelial dysfunction typically involve oxidative stress, inflammation, and disruptions in eNOS function (Higashi, 2022; Nguyen et al., 2023; Roy et al., 2023; Shaito et al., 2022).

One significant factor contributing to eNOS-related endothelial dysfunction is eNOS uncoupling. In the presence of oxidative stress or a lack of essential cofactors like tetrahydrobiopterin (BH4), eNOS can become "uncoupled," leading to the production of reactive oxygen species (ROS) instead of NO. This uncoupling not only diminishes NO production but also contributes to further endothelial damage and promotes vascular inflammation. Additionally, oxidative stress itself leads to the degradation of NO, further reducing its bioavailability and disrupting vascular homeostasis. These mechanisms highlight the critical role of eNOS in maintaining endothelial function and the consequences of its dysfunction (Higashi, 2022; Li et al., 2016; Tran et al., 2022).

SCUBE1, a multifunctional protein involved in adhesion, signaling, and angiogenesis, is a promising biomarker for endothelial dysfunction and platelet activation. Elevated in atherosclerosis, stroke, and coronary artery disease, it reflects vascular injury and promotes inflammation, coagulation, and platelet-endothelium interactions. Normally, eNOS-derived nitric oxide (NO) maintains vascular tone, inhibits platelet adhesion, and limits inflammation. Reduced NO in oxidative stress-related conditions triggers platelet activation and SCUBE1 release, which amplifies vascular injury in a feedback loop. Targeting eNOS to restore NO production and inhibiting SCUBE1 pathways may help reduce thrombosis, inflammation, and endothelial damage in cardiovascular disease (Akdoğan et al., 2019; Kok et al., 2023; Sharma et al., 2015).

eNOS and endothelial dysfunction

The addressing of this mechanism by Lamas et al. occurred in the context of estrogen deprivation, a critical factor in postmenopausal vascular decline. Using an ovariectomized rodent model, they demonstrated that estrogen replacement and selective estrogen receptor modulators (SERMs) notably raloxifene and tamoxifen effectively restored endothelium-dependent vasorelaxation. The improvements seen were the result of a balance between two different nitric oxide pathways: vasoprotective and proinflammatory. This balance was restored through the process of normalization of eNOS expression and suppression of inducible nitric oxide synthase (iNOS). Additionally, antioxidative effects were exerted by raloxifene, and inflammatory mediators such as TNF-α and IL-6 were attenuated by both SERMs, thereby underscoring their therapeutic potential in modulating endothelial homeostasis under hypoestrogenic conditions (Lamas et al., 2015).

In a separate investigation, Takahashi et al. examined eNOS functionality in ischemia-driven angiogenesis, focusing on metformin as a pharmacological modulator. In experiments with mice that had their back legs cut off, metformin significantly improved blood flow and the growth of new blood vessels. These effects depended on the health of a certain protein called eNOS. While adenosine monophosphate-activated protein kinase (AMPK) was active in both normal and eNOS-deficient mice, only the normal mice had new blood vessels. This shows that metformin's ability to cause new blood vessels to form depends on eNOS signaling working properly (Takahashi et al., 2015).

Together, these findings highlight the importance of eNOS in endothelial adaptation across various pathological states. Pharmacological strategies that augment eNOS expression or activity, whether through estrogenic pathways or metabolic agents like metformin, may be pivotal in mitigating endothelial dysfunction and preserving vascular health in at-risk populations (Lamas et al., 2015; Takahashi et al., 2015).

eNOS and therapeutic regulation

The endothelial isoform of nitric oxide synthase (eNOS) is essential for maintaining vascular homeostasis. Nitric oxide (NO) is a key molecule that modulates endothelial proliferation, angiogenic capacity, barrier integrity, and vascular tone. Chakraborty et al. (2017) identified a mechanism by which NOSTRIN (nitric oxide synthase trafficking

inducer) decreases eNOS activity by promoting its intracellular sequestration and reducing NO availability. This post-translational modulation hinders endothelial cell migration and tubulogenesis and intersects with innate immune pathways via NOSTRIN's interaction with TRAF6. This interaction inhibits NF-κB signaling. Such dual impairment of vasoreparative and anti-inflammatory signaling cascades underscores the pathogenic relevance of NOSTRIN overexpression in disorders like preeclampsia, wherein heightened NOSTRIN expression correlates with vascular constriction and systemic endothelial dysfunction (Chakraborty & Ain, 2017).

Additionally examining the regulatory framework of eNOS, Xu et al. (2017) clarified a mechanotransductive sequence triggered by laminar shear stress, a biological signal vital for endothelial well-being. Central to this process is PECAM1-mediated transduction that initiates the phosphorylation of Gab1, which in turn activates the PI3K-Akt axis, culminating in the phosphorylation and activation of eNOS. The signaling pathway's integrity is crucial for the endothelium's ability to adapt to hemodynamic forces, which in turn facilitates NO-mediated vasoprotection. Perturbations in flow-induced signaling commonly observed at arterial bifurcations or in regions of disturbed flow contribute to spatially confined endothelial dysfunction and are mechanistically linked to atheroprone vascular regions. Thus, the data from Xu et al. provide critical insight into the biomechanical control of endothelial phenotype and its breakdown under pathological flow conditions.(S. Xu et al., 2017)

On a genetic and receptor-mediated signaling level, Fredette et al. (2020) explored the implications of GPER (G protein-coupled estrogen receptor) polymorphisms in modulating eNOS activity and vascular tone. The study used endothelial-specific knockout models to show that loss of GPER function impairs eNOS-derived NO production, independent of SNP-related coding alterations. This suggests that intact GPER signaling is required for estrogen-dependent vasodilatory responses. The findings point to the potential for receptor-level modulation in cardiovascular risk stratification and therapy, given the sex-specific prevalence and progression of hypertensive phenotypes. Importantly, the data suggest that even in the absence of pathogenic SNP effects, the functional integrity of GPER remains essential to preserve endothelial responsiveness, offering new avenues for sex-specific therapeutic interventions in hypertension.(Chakraborty & Ain, 2017; S. Xu et al., 2017)

eNOS and The Pathways

Endothelial nitric oxide synthase (eNOS) is a constitutive enzyme responsible for the biosynthesis of nitric oxide (NO), a gaseous signaling molecule crucial for vasomotor regulation, antithrombotic activity, and the maintenance of vascular integrity. Perturbation of eNOS function, particularly under oxidative stress conditions, compromises NO bioavailability, resulting in impaired endothelial-dependent vasodilation and augmented leukocyte adhesion. Ling Xu et al. (2021) demonstrated that oxidized low-density lipoprotein (ox-LDL), a known atherogenic mediator, significantly suppresses eNOS expression while concurrently upregulating inducible nitric oxide synthase (iNOS) in human umbilical vein endothelial cells (HUVECs). This dysregulation precipitates an imbalance in NO synthesis and leads to excessive peroxynitrite generation, thus promoting oxidative injury and endothelial dysfunction—hallmarks in the pathogenesis of atherosclerosis.(L. Xu et al., 2021)

The study by Xu et al. further elucidates a mechanistic link between ox-LDL exposure and the upregulation of (20lysophosphatidic acid receptor 5 (LPAR5), a G protein-coupled receptor implicated in vascular inflammation. Targeted silencing of LPAR5 was shown to mitigate endothelial dysfunction by restoring eNOS expression and enhancing NO synthesis, thus attenuating endothelial oxidative burden. Moreover, suppression of LPAR5 expression reduced the activation of the NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome, a cytosolic sensor associated with pro-inflammatory cytokine maturation and endothelial injury. These findings suggest a dual role of LPAR5 in modulating both NO signaling and inflammatory cascades, indicating its potential as a therapeutic target

for ameliorating ox-LDL-induced vascular pathology.(L. Xu et al., 2021)

Endothelial dysfunction is a critical determinant of cardiovascular risk and serves as a unifying mechanism linking hypertension, hyperlipidemia, and metabolic disturbances to vascular disease progression. Reduced eNOS-derived NO availability is frequently exacerbated by chronic oxidative stress and inflammatory signaling, resulting in eNOS uncoupling and reactive oxygen species (ROS) overproduction. In this context, studies such as those by Zhan et al. (2020) have demonstrated that agents like nicorandil can modulate the PI3K/Akt/eNOS axis, promoting eNOS phosphorylation and restoring endothelial NO output under hyperhomocysteinemic conditions. Similarly, Stamm et al. (2021) reported that inorganic nitrite administration reestablishes NO homeostasis by enhancing eNOS activity and reducing oxidative burden. Collectively, these interventions underscore the therapeutic relevance of targeting eNOS modulation in vascular medicine, offering pharmacological and nutraceutical avenues to restore endothelial function and halt atherosclerotic progression.(Stamm et al., 2021; Zhan et al., 2020)

SCUBE1 and Endothelial Dysfunction

SCUBE1 (Signal peptide-CUB-EGF-like domain-containing protein 1), primarily derived from platelets, plays a multifaceted role in the pathophysiology of thrombus formation, platelet activation, and endothelial interaction. Research conducted by Bilir et al. (2016) and Bolayir et al. (2017) has elucidated the upregulation of SCUBE1 in pathologic settings characterized by endothelial dysfunction, systemic inflammation, and tissue hypoxia.(Bilir et al., 2016; Bolayır et al., 2017) Topcu et al. (2015) observed that heightened SCUBE1 concentrations correlate with an increased incidence of thrombotic events, including acute coronary syndromes, ischemic cerebrovascular insults, and other atherothrombotic cardiovascular diseases, thereby supporting its potential diagnostic and prognostic significance in vascular medicine (Topcu et al., 2015)

In endocrine-related inflammatory disorders such as Hashimoto's thyroiditis, SCUBE1 concentrations were found to be significantly elevated relative to normothyroid individuals, indicating a plausible link between autoimmune hypothyroidism and subclinical atherogenesis through endothelial damage and platelet activation. The concomitant elevation of SCUBE1 and soluble CD40 ligand (sCD40L), a well-established inflammatory and thrombotic mediator, further supports its involvement in endothelial impairment and plaque instability in these patients. Such biochemical associations underscore the potential utility of SCUBE1 in identifying vascular risk among patients with chronic autoimmune and metabolic dysregulation.(Bilir et al., 2016)

Beyond classic cardiovascular scenarios, SCUBE1 expression has also been implicated in oncologic pathology. Elevated SCUBE1 levels have been documented in patients with malignancies, including breast carcinoma, suggesting its relevance in cancer-associated thrombosis and systemic hypercoagulability.(Topcu et al., 2015) In the context of ST-elevation myocardial infarction (STEMI), Bolayir et al. (2017) demonstrated that increased SCUBE1 was significantly associated with the no-reflow phenomenon following percutaneous coronary intervention, indicating its predictive value in microvascular obstruction despite angiographic success. Taken together, these data position SCUBE1 as a novel biomarker integrating endothelial integrity, platelet dynamics, and thrombotic burden across diverse clinical entities, warranting further investigation into its translational applications in cardiovascular and systemic disease stratification.(Bolayır et al., 2017)

SCUBE1 and Vascular Health

SCUBE1 (Signal peptide-CUB-EGF domain-containing protein 1) has emerged as a significant biomarker in vascular health and endothelial dysfunction across various diseases, including psoriasis, ischemic injuries, and pulmonary arterial hypertension (PAH). Its role is closely tied to endothelial integrity, angiogenesis, and the body's response to vascular stress.(Sun et al., 2020)

SCUBE1 and Atherosclerosis: In psoriasis patients, who are at heightened risk for cardiovascular diseases, SCUBE1 levels were significantly elevated compared to healthy controls. The study by Ayvaz Çelik et al. (2023) demonstrated that SCUBE1 correlates positively with carotid artery

intima-media thickness (CIMT), a marker of subclinical atherosclerosis. This suggests that SCUBE1 might serve as an early indicator of cardiovascular risk in inflammatory conditions like psoriasis, even before the onset of overt clinical symptoms. The protein's association with angiogenesis and endothelial dysfunction reinforces its potential as a predictive marker for atherosclerosis .(Ayvaz Çelik et al., 2023)

SCUBE1 in Ischemia-Reperfusion Injury: Sogut et al. (2017) highlighted the role of SCUBE1 in ischemia-reperfusion injury. Although SCUBE1 levels do not rise during ischemia, they increase significantly during reperfusion, marking its relevance in endothelial recovery and platelet activation. This indicates that SCUBE1 may not be suitable for early detection of ischemia but could be valuable for assessing reperfusion and tissue recovery post-injury. In ischemia-reperfusion contexts, SCUBE1 reflects endothelial cell responses to hypoxia, linking it to endothelial damage and subsequent repair .(Sogut et al., 2017)

SCUBE1 plays a critical role in pulmonary arterial hypertension (PAH), a condition marked by pronounced endothelial dysfunction. Sun et al., (2020) demonstrated that SCUBE1 regulates the BMPR2 signaling pathway, essential for maintaining pulmonary vascular integrity. In PAH, reduced SCUBE1 expression correlates with greater endothelial damage, impaired angiogenesis, and diminished endothelial proliferation, all contributing to pulmonary vascular remodeling. This downregulation is closely linked to disease progression, positioning SCUBE1 as a promising diagnostic biomarker that reflects both vascular injury and functional impairment, offering potential for early detection and assessment of PAH severity based on measurable molecular changes.(Sun et al., 2020)

Beyond PAH, SCUBE1 is involved in a wide spectrum of cardiovascular and systemic disorders characterized by endothelial dysfunction. It modulates platelet activation, angiogenesis, and vascular responses to hypoxia and inflammation—pathways central to diseases such as atherosclerosis, ischemia-reperfusion injury, and systemic inflammatory conditions like psoriasis. SCUBE1 consistently rises under endothelial stress, underscoring its potential as a reliable diagnostic and prognostic marker. Its broad involvement in endothelial biology suggests value in risk stratification, monitoring disease progression, and serving as a therapeutic target, particularly in vascular pathologies where endothelial integrity and angiogenic balance are disrupted.(Ali, 2024; Lin et al., 2023)

Conclusion

In this systematic review, eNOS-enhancing interventions consistently increased nitric oxide bioavailability, improved endothelium-dependent vasorelaxation, and lowered oxidative stress, supporting eNOS-oriented indices as therapeutic targets and response markers in endothelial dysfunction; SCUBE1 emerged as a thrombo-inflammatory signal that rises across prothrombotic, autoimmune, oncologic, and ischemia–reperfusion contexts, tracks microvascular obstruction in acute coronary settings, and is reduced in pulmonary arterial hypertension where it links to BMPR2 pathway integrity, indicating utility for triage, risk stratification, and diagnostic support across distinct disease states, provided matrices and cut-offs are standardized before routine adoption.

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