# REVIEW

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## ENDOTHELIAL GLYCOCALYX INTEGRITY IN HEALTH AND DISEASE: MOLECULAR MECHANISMS AND STRESS-RELATED VASCULAR INJURY

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***Background.*** *The endothelial glycocalyx (EGX) is a dynamic carbohydrate-rich structure located at the blood-endothelium interface that regulates vascular permeability, mechanotransduction, inflammation, coagulation, and endothelial signaling. Its complex molecular architecture makes the EGX highly susceptible to enzymatic degradation, oxidative stress, and inflammatory mediators, making its disruption a key mechanism of endothelial dysfunction in diverse pathological conditions.* ***Objective.*** *To synthesize current evidence on the molecular architecture of the endothelial glycocalyx, the biochemical mechanisms underlying its degradation, its role in cardiovascular and stress-associated disorders, and emerging glycocalyx-targeted therapeutic strategies.* ***Methods.*** *This integrative review synthesizes evidence from 93 scientific studies identified through a systematic search of ten electronic databases.* ***Results.*** *The analysis demonstrates that glycocalyx degradation contributes to impaired endothelial nitric oxide signaling, increased vascular permeability, endothelial inflammation, and microvascular dysfunction in cardiovascular pathology. Recent evidence further suggests that chronic psychological stress and post-traumatic stress disorder may promote EGX disruption through sustained sympathetic activation, oxidative stress, and low-grade inflammation. The review also discusses therapeutic strategies aimed at preserving or restoring glycocalyx integrity, including inhibition of enzymatic degradation and glycocalyx-targeted regenerative approaches.* ***Conclusions.*** *These findings support a shift toward targeting the glycocalyx as an upstream regulator of vascular health rather than exclusively focusing on downstream vascular complications.*

*K e y w o r d s: endothelial glycocalyx, vascular permeability, glycocalyx shedding, cardiovascular disease, post-traumatic stress disorder.*

The vascular endothelium represents a highly specialized regulatory interface that integrates mechanical, biochemical, and immunological signals to maintain tissue perfusion and systemic homeostasis. At the blood-endothelium interface lies the endothelial glycocalyx (EGX), a specialized gel-like layer composed of proteoglycans, glycosaminoglycans, glycoproteins, and associated plasma proteins [1-3]. Rather than acting as a passive surface coating, the EGX regulates multiple vascular functions discussed in this review.

By reversibly binding plasma proteins such as albumin, the EGX contributes to the formation of the endothelial surface layer (ESL), an interface that stabilizes the vascular barrier and modulates microcirculatory flow [4]. Disruption of this structure is increasingly recognized as a common feature of diverse pathological conditions including sepsis, trauma, and ischemia-reperfusion injury, in which it is associated with endothelial dysfunction, increased permeability, and inflammation [5-7].

The EGX undergoes continuous remodeling in response to shear stress, enzymatic activity, and inflammatory signaling. Accumulating evidence indicates rapid, context-dependent alterations in glycocalyx thickness and composition, highlighting its

sensitivity to systemic stressors and its potential as a therapeutic target [8, 9]. In addition, pronounced organ-specific heterogeneity of the glycocalyx reflects adaptation to local physiological demands.

While inflammatory and hemodynamic mechanisms of EGX disruption are well established, the contribution of neuroendocrine stress remains insufficiently explored [10-13]. We further propose that stress-related neuroendocrine dysregulation constitutes an underexplored driver of EGX injury.

The purpose of this review is to conceptualize the EGX as an integrative interface of mechanical, inflammatory, and neuroendocrine signals for vascular function. We further propose that stress-induced glycocalyx degradation contributes to endothelial dysfunction and cardiovascular risk, as a part of an integrated EGX-endothelium-immune glycan axis.

## Review Methodology

This review was conducted as an integrative literature review, aiming to generalize 93 scientific studies on the molecular mechanisms and the role of EGX integrity in health and disease. The search strategy employed a combination of 52 controlled vocabulary terms and free-text keywords, using Boolean operators (AND, OR). The main search terms were: glycocalyx; vascular permeability; glycocalyx shedding; cardiovascular disease; post-traumatic stress disorder (PTSD).

Original studies, review articles, and patents published in English were included, focusing on the molecular structure, functional roles, and regulatory mechanisms of the EGX, as well as its involvement in endothelial dysfunction, cardiovascular disease, trauma, and stress-related conditions, including PTSD. Publication Period: Priority was given to literature published in the last 10 years (2015-2026), with inclusion of classic and fundamental articles from earlier periods, based on their relevance. Exclusion Criteria: conference abstracts, letters to the editor, and articles that did not directly address the molecular mechanisms, functional significance, or pathological alterations of the endothelial glycocalyx were excluded. The article selection was performed in two stages: (1) initial screening by title and abstract; and (2) full-text reading of pre-selected articles to confirm eligibility.

## 1. Structural components of the endothelial glycocalyx

The EGX is a structurally complex interface composed of multiple classes of macromolecules that collectively determine its mechanical properties and biological functions (Fig. 1). Its major components include proteoglycans, glycoproteins, glycosaminoglycans, glycosphingolipids, and plasma proteins, which interact synergistically to maintain glycocalyx integrity and function [3, 14].

Proteoglycans (PGs) constitute the principal structural framework of the EGX and function as key regulators of endothelial signaling. They consist of core proteins covalently linked to glycosaminoglycan chains, whose length, sulfation, and spatial organization determine binding affinity for plasma proteins, cytokines, and growth factors [15, 16].

Among endothelial PGs, syndecans (1-4) and glypicans (1-6) represent the major membrane-associated families, each contributing distinct regulatory functions.

Syndecans are transmembrane PGs composed of an extracellular ectodomain, a single-pass transmembrane domain, and a cytoplasmic tail that interacts with intracellular signaling machinery. Their ectodomains carry heparan sulfate and, in some isoforms, chondroitin sulfate chains, enabling interactions with extracellular matrix components and circulating mediators [17, 18]. Through their cytoplasmic domains, syndecans couple extracel-

**Abbreviations.** ADAMs – A Disintegrin and Metalloproteinases; ATIII – Antithrombin III; CAMs – Cell Adhesion Molecules; CD44 – Cluster of Differentiation 44 (cell adhesion receptor for hyaluronan); CS – Chondroitin Sulfate; CVD – Cardiovascular Disease; DS – Dermatan sulfate; EGX – Endothelial Glycocalyx; ESL – Endothelial Surface Layer; eNOS – Endothelial Nitric Oxide Synthase; GAGs – Glycosaminoglycans; GPs – Glycoproteins; GPC – Glypican; HA – Hyaluronan / Hyaluronic Acid; HFpEF – heart failure with preserved ejection fraction; HPSE – Heparanase; HPA axis – Hypothalamic-Pituitary-Adrenal axis; HS – Heparan Sulfate; ICAM-1 – Intercellular Adhesion Molecule-1; IgG – Immunoglobulin G; KS – Keratan sulfate; LDL – Low-Density Lipoprotein; LPS – Lipopolysaccharide; MMPs – Matrix Metalloproteinases; NF-κB – Nuclear Factor kappa-light-chain-enhancer of activated B cells; NO – Nitric Oxide; PAMPs – Pathogen-Associated Molecular Patterns; PGs – Proteoglycans; PTSD – Post-Traumatic Stress Disorder; S1P – Sphingosine-1-phosphate; TIMPs – Tissue Inhibitors of Metalloproteinases; TNF-α – Tumor Necrosis Factor alpha; VCAM-1 – Vascular Cell Adhesion Molecule-1; VEGF – Vascular Endothelial Growth Factor.

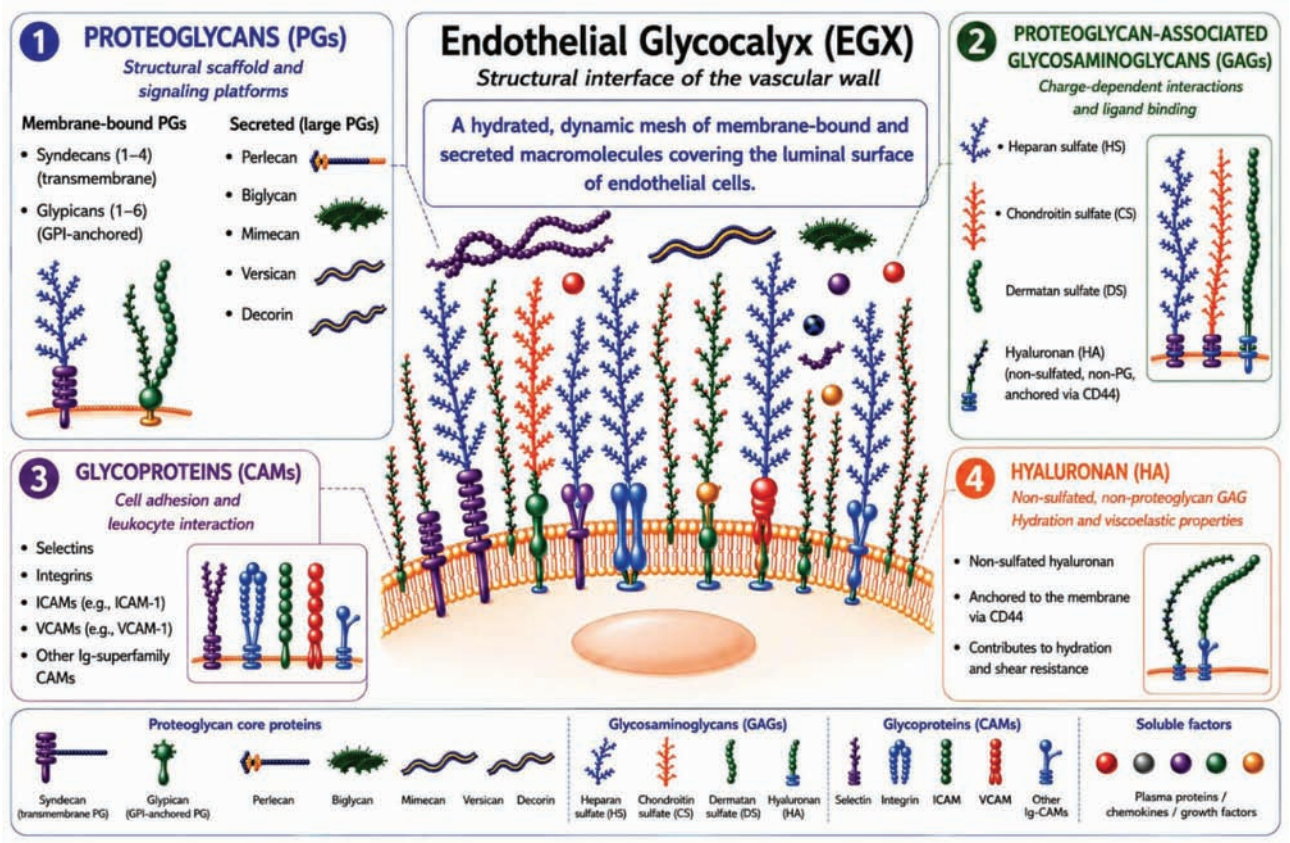


*Fig. 1. Structural and functional organization of the endothelial glycocalyx (EGX). Schematic representation of the luminal endothelial surface showing membrane-bound proteoglycans (syndecans, glypicans) bearing heparan sulfate and chondroitin sulfate chains, hyaluronan anchored via Cluster of Differentiation 44 (CD44), and glycoproteins including adhesion molecules. Secreted proteoglycans and plasma proteins contribute to the formation of the endothelial surface layer*

lular cues to intracellular pathways, linking ligand binding to cytoskeletal organization and kinase-dependent signaling [19].

Experimental evidence demonstrates that syndecan-mediated signaling regulates endothelial barrier integrity and leukocyte recruitment. Under inflammatory conditions, syndecan-1 shedding modulates leukocyte-endothelium interactions through chemokine availability and integrin-dependent adhesion, contributing either to resolution of inflammation or to vascular dysfunction depending on context [20-22]. In addition, modulation of syndecan expression alters endothelial responses to cytokines and shear stress, supporting its role as a context-dependent signaling regulator [23-24].

Glypicans (GPC), in contrast, are glycosylphosphatidylinositol-anchored PGs located in membrane microdomains such as caveolae [25, 26]. GPC-1 plays a central role in mechanotransduction by facilitating shear stress-induced activation of endothelial nitric oxide synthase (eNOS) [27, 28]. The malfunctioning of GPC-1 or enzymatic degradation of heparan sulfate impairs flow-mediated nitric oxide (NO) production, demonstrating a direct link between glycocalyx integrity and endothelial mechanosensing [29, 30]. In experimental models, GPC-1 deficiency alters glycocalyx architecture and reduces eNOS phosphorylation, further supporting its role in flow-dependent signaling [29].

In addition to membrane-bound PGs, large extracellular PGs such as perlecan, decorin, and versican contribute to glycocalyx organization and interactions with plasma proteins [3, 31-33]. In summary, PGs function as signaling platforms that integrate mechanical and inflammatory cues and are highly susceptible to enzymatic shedding during pathological conditions.

Glycosaminoglycans (GAGs) are linear, negatively charged polysaccharides composed of re-

peating disaccharide units of uronic acids and hexosamines. Their sulfation and acetylation generate substantial structural heterogeneity, which determines ligand-binding specificity and signaling functions [34].

Heparan sulfate (HS) is the predominant glycocalyx GAG, accounting for approximately 50–90% of proteoglycan-associated chains. It consists of alternating uronic acid residues (β-D-glucuronic acid or α-L-iduronic acid) and glucosamine derivatives that undergo extensive N- and O-sulfation [35, 36]. HS chains are organized into distinct sulfation domains that govern binding to growth factors, chemokines, and coagulation-related proteins, thereby regulating endothelial signaling, vascular permeability, and inflammatory responses [37]. Experimental evidence shows that HS-dependent interactions modulate growth factor activity, particularly in VEGF-related pathways [ 20, 38, 39]. Moreover, enzymatic degradation of HS (e.g., by heparinase) impairs mechanotransduction and reduces shear stress-induced nitric oxide production, highlighting its central role in endothelial signaling [40].

Chondroitin sulfate (CS) and dermatan sulfate (DS) contribute to glycocalyx structure and function. Both consist of repeating disaccharide units containing N-acetylgalactosamine and uronic acids. On the other hand, DS is characterized by epimerization of glucuronic acid to iduronic acid, which increases chain flexibility and interaction potential. CS has been shown to enhance barrier properties of extracellular matrices, supporting its role in vascular barrier regulation [41].

Keratan sulfate (KS) is less abundant and composed of repeating galactose and N-acetylglucosamine units with variable sulfation. Recent studies indicate that altered KS metabolism may contribute to chronic inflammatory microenvironments through modulation of TLR4/NF-κB-dependent signaling and chemokine expression, although these mechanisms remain insufficiently characterized in the vascular endothelium [42].

Hyaluronan (HA) is unique among GAGs as a non-sulfated, non-proteoglycan-associated polymer synthesized at the plasma membrane. It forms highly hydrated networks that contribute to glycocalyx viscoelasticity and interacts with CD44 to regulate leukocyte adhesion and inflammatory signaling [43]. Experimental studies indicate that HA-CD44 interactions facilitate leukocyte recruitment within inflamed vascular beds [44].

Thus, GAGs serve not only as structural components of the glycocalyx but also play an active role in regulating endothelial signaling. Their sulfation patterns influence interactions with proteins and contribute to the control of mechanotransduction and inflammatory responses [34].

Glycoproteins (GPs) within the EGX carry short, branched carbohydrate chains typically attached via N- or O-linked glycosylation. These glycans contribute to protein stability, ligand recognition, and receptor-ligand specificity, thereby regulating cell-cell and cell-matrix interactions [45].

A major functional class comprises cell adhesion molecules (CAMs), including selectins (E- and P-selectin), integrins (e.g., αVβ3), and members of the immunoglobulin superfamily (ICAM-1, VCAM-1, PECAM-1). Together, these molecules coordinate leukocyte rolling, firm adhesion, and transendothelial migration, forming the molecular basis of vascular inflammatory responses [46-48].

Selectins mediate transient leukocyte tethering through carbohydrate-dependent interactions, thereby initiating leukocyte rolling along the endothelial surface. Subsequent integrin activation promotes firm adhesion and intracellular signaling, while immunoglobulin-like CAMs coordinate controlled leukocyte transmigration and maintenance of endothelial barrier integrity under physiological conditions. [47]. In inflammatory vascular conditions, increased expression of selectins, particularly E-selectin, reflects endothelial activation and contributes to leukocyte recruitment and vascular dysfunction [49].

In addition to PGs and GPs, the EGX contains glycosphingolipids and reversibly bound plasma proteins. Glycosphingolipids contribute to the formation of membrane microdomains, thereby influencing receptor localization, membrane organization, and intracellular signal transduction. Recent experimental evidence further suggests that altered sphingolipid signaling, particularly involving ceramides and sphingosine-1-phosphate (S1P), contributes to endothelial dysfunction and vascular pathology. Plasma proteins such as albumin and antithrombin modulate glycocalyx thickness, charge, and barrier properties [50]. Together, membrane-bound glycocalyx components, glycosphingolipid-rich membrane domains, and reversibly associated plasma proteins contribute to the formation of the ESL, whose thick-

ness (approximately 0.5–4.5 μm) varies depending on vessel type and physiological conditions.

## 2. Functions of the endothelial glycocalyx

First, the glycocalyx serves as a size- and charge-selective barrier, limiting the passage of plasma proteins and regulating fluid exchange. Negatively charged components, HS, play a key role in maintaining endothelial junction integrity and vascular permeability (Fig. 2) [51, 52].

Second, the EGX regulates interactions between circulating blood elements and the vessel walls [48, 53].

Third, the glycocalyx functions as a mechanosensory interface. Shear stress generated by blood flow is transmitted through glycocalyx-associated molecules, leading to activation of eNOS, NO production, and regulation of vascular tone and blood pressure [51].

Fourth, the EGX contributes to anticoagulant and antithrombotic balance by binding proteins such as antithrombin III (ATIII) and masking procoagulant endothelial surfaces, thereby limiting platelet adhesion and fibrin formation [52].

Finally, the glycocalyx acts as a dynamic reservoir for bioactive molecules, including chemokines, growth factors, and plasma proteins. By concentrating these ligands it enhances signaling efficiency and modulates inflammatory responses [3].

## 3. Mechanisms of glycocalyx degradation and remodeling

The EGX undergoes continuous remodeling through a balance between biosynthesis, enzymatic degradation, and mechanical shedding. Biosynthesis of glycocalyx components occurs in the endoplasmic reticulum and Golgi apparatus, where PGs and GAG chains are assembled and modified. These processes generate structurally diverse glycoconjugates whose sulfation patterns determine binding specificity for growth factors, chemokines, and coagulation-related proteins.

In contrast, glycocalyx degradation may occur rapidly and is strongly influenced by inflammatory signaling, enzymatic activity, and oxidative stress. Under pathological conditions, these processes promote accelerated shedding and structural disruption of the EGX. Importantly, glycocalyx degradation

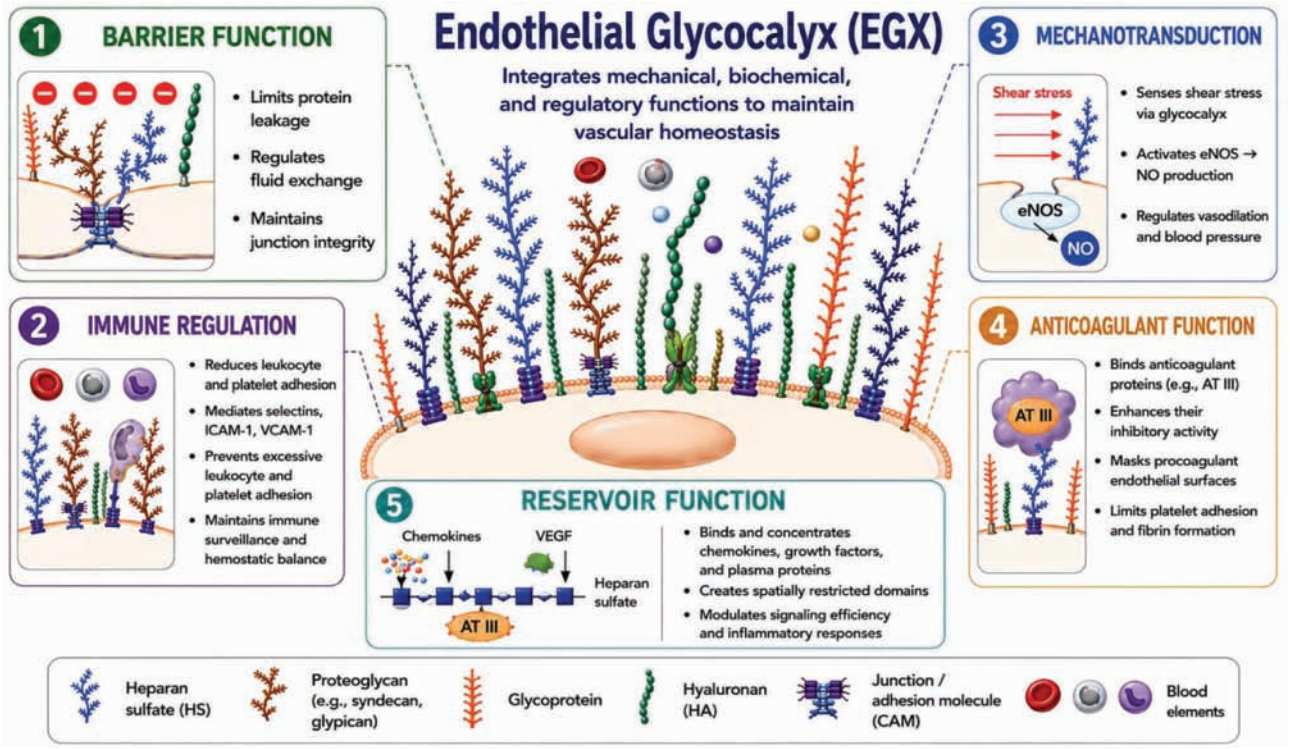


*Fig. 2. Functional roles of the endothelial glycocalyx (EGX). Diagram illustrating key EGX functions, including regulation of vascular permeability, shielding of adhesion molecules, mechanotransduction of shear stress leading to eNOS activation and nitric oxide production, maintenance of anticoagulant properties, and binding of circulating signaling molecules*

can be induced much more rapidly than its restoration, which explains why shedding and degradation are considered major drivers of acute glycocalyx remodeling. Among these mechanisms, protease-mediated ectodomain shedding represents a key pathway linking inflammatory and mechanical stimuli to rapid structural and functional alterations of the endothelial surface layer [55].

Ectodomain shedding is a principal mechanism of EGX turnover, rapidly altering the surface presentation of membrane-bound PGs, GPs, and adhesion molecules. As a result, it directly influences leukocyte–endothelium interactions, vascular permeability, coagulation, and vascular tone.

Shedding is primarily mediated by matrix metalloproteinases (MMPs) and members of the ADAM/ADAMTS family, which cleave extracellular domains of key glycocalyx components, including syndecans and adhesion molecules such as ICAM-1, a process that is present under physiological conditions but markedly accelerated during inflammation, oxidative stress, ischemia–reperfusion injury, and cytokine exposure [56-58]. Protease activity is tightly regulated by tissue inhibitors of metalloproteinases (TIMPs), particularly TIMP-1 and TIMP-3, which contribute to the control of glycocalyx remodeling. This balance ensures spatiotemporal regulation of protease activity; however, under pathological conditions, it becomes disrupted, leading to excessive glycocalyx shedding [59].

In addition to biochemical regulation, mechanical forces contribute to glycocalyx remodeling. Shear stress can modulate protease activity, linking hemodynamic forces to structural alterations of the endothelial surface. Loss of glycocalyx components, particularly HS, impairs NO production and endothelial mechanotransduction, underscoring the functional consequences of shedding [60].

Clinically, excessive glycocalyx shedding is observed in trauma and hemorrhagic shock, where it is associated with a transition from an anti-inflammatory, anticoagulant endothelial surface to a pro-inflammatory and pro-thrombotic phenotype [61]. This shift is accompanied by increased vascular permeability, enhanced cytokine interactions, oxidative stress, and microvascular dysfunction, and correlates with adverse outcomes.

Circulating biomarkers of shedding, including syndecan-1, HA, and HS, provide indirect measures of glycocalyx degradation. Among these, syndecan-1 is the most extensively studied and correlates with the severity of endothelial injury and clinical prognosis [14, 62].

Protease-mediated shedding connects mechanical, inflammatory, and biochemical signals with rapid glycocalyx remodeling. Although it may be adaptive in acute settings, prolonged activation promotes endothelial dysfunction and disease progression.

In addition to proteolytic shedding, glycocalyx remodeling also occurs through enzymatic degradation of GAG chains. Enzymes such as heparanase, hyaluronidases, and endosulfatases cleave or modify GAGs, altering the structural and electrostatic properties of the glycocalyx and reducing its capacity to bind signaling molecules [15].

Heparanase is a key mediator of HS degradation and is upregulated by inflammatory cytokines and oxidative stress. Endosulfatases (Sulf-1 and Sulf-2) selectively remove sulfate groups from HS, modifying its interactions with growth factors and chemokines, while hyaluronidases regulate HA turnover [63].

Importantly, enzymatic degradation of GAGs not only alters the structural integrity of the glycocalyx but also disrupts its regulatory functions, including barrier properties, mechanotransduction, and inflammatory signaling.

### 4. EGX dysfunction in disease

Despite its essential role in vascular homeostasis, the EGX is a fragile structure highly susceptible to inflammatory and oxidative injury. Glycocalyx degradation has been observed in a broad range of pathological conditions, including sepsis, diabetes, chronic kidney disease, hypertension, atherosclerosis, cardiovascular disease, and COVID-19 [64, 65].

Activation of inflammatory pathways, particularly via TNF-α signaling, can induce rapid EGX collapse through upregulation of proteases and glycosidases [66]. In acute infection, this response promotes controlled interactions between the endothelium, leukocytes, and platelets, supporting pathogen clearance and tissue repair. In systemic inflammation, pathogen-associated molecular patterns (PAMPs), such as lipopolysaccharide (LPS), activate Toll-like receptor signaling, promoting glycocalyx degradation. Experimental evidence indicates that inflammatory activation enhances shedding of glycocalyx components through protease- and oxidative stress–dependent mechanisms [56, 62, 67] (Fig. 3).

Similar mechanisms have also been described in COVID-19, where elevated circulating syndecan-1

levels are associated with endothelial dysfunction, disease severity, and adverse clinical outcomes, further supporting the role of glycocalyx injury in systemic inflammatory conditions [68]. SARS-CoV-2 demonstrates pronounced endothelial tropism mediated through ACE2, TMPRSS2, CD147, and neuropilin-1 signaling pathways, contributing to endothelial dysfunction, inflammatory activation, and microvascular injury, which are considered central mechanisms of vascular complications associated with COVID-19 [69]. In addition, recent clinical studies support the involvement of inflammatory and profibrotic pathways in cardiovascular complications associated with COVID-19 and arterial hypertension [70].

In contrast, persistent exposure to inflammatory, metabolic, or mechanical stress results in chronic glycocalyx disruption. This state is characterized by sustained shedding, impaired regeneration, and a shift toward a pro-inflammatory and prothrombotic endothelial phenotype. In cardiovascular disease (CVD), EGX disruption functions both as a contributor to and as a consequence of pathological vascular remodeling [71].

Hemodynamic stress is considered one of the major factors contributing to glycocalyx remodeling. Disturbed flow patterns, sustained shear stress, and elevated transmural pressure promote enzymatic degradation and impair glycocalyx synthesis. These changes disrupt endothelial mechanotransduction, reduce nitric oxide bioavailability, and favor vasoconstriction. Loss of HS and other GAGs further compromises barrier function, facilitating low-density lipoprotein (LDL) infiltration and early atherogenic changes [9, 71].

Glycocalyx degradation also contributes to the early stages of atherosclerosis. Increased endothelial permeability facilitates lipid retention within the vascular wall, while impaired mechanotransduction and reduced nitric oxide signaling promote endothe-

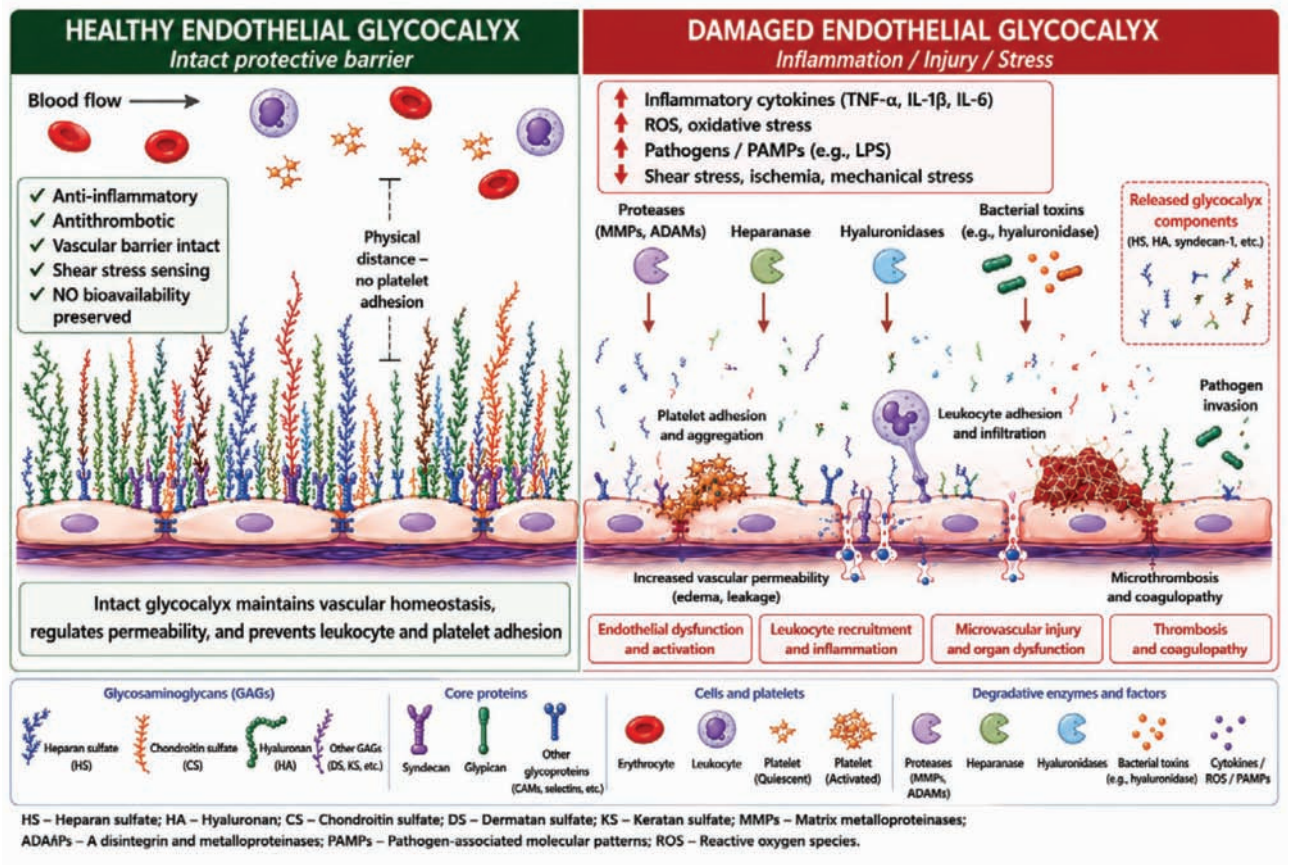


*Fig. 3. Endothelial glycocalyx (EGX) in physiological and inflammatory conditions. Comparison of intact and degraded glycocalyx. Under physiological conditions, the EGX forms a continuous barrier limiting permeability and cell adhesion. In inflammation, activation of proteases and glycosidases leads to glycocalyx thinning and shedding, resulting in increased permeability, leukocyte adhesion, and platelet activation*

lial activation and vascular dysfunction [72, 73]. In parallel, exposure of adhesion molecules such as VCAM-1 and ICAM-1 enhances leukocyte adhesion and transmigration, sustaining chronic vascular inflammation and progression of atherosclerotic remodeling [74].

Inflammatory signaling further amplifies EGX injury. Cytokines such as TNF-α and IL-6 activate sheddases, including MMPs, ADAMs, and heparanase, thereby accelerating glycocalyx degradation and perpetuating vascular inflammatory responses.

Myocardial ischemia-reperfusion injury represents a setting of rapid and pronounced EGX disruption. Reperfusion-induced oxidative stress and inflammatory activation lead to acute glycocalyx loss, contributing to capillary leak, microvascular obstruction, and platelet activation. Experimental models demonstrate that EGX shedding occurs within minutes and is associated with impaired microvascular perfusion, whereas preservation of the glycocalyx improves vascular integrity and limits tissue injury [75-77].

In chronic heart failure, particularly heart failure with preserved ejection fraction (HFpEF), sustained neurohormonal activation, comorbidity-driven low-grade inflammation, and oxidative stress maintain persistent glycocalyx injury [75]. Current concepts of HFpEF pathophysiology emphasize coronary microvascular endothelial dysfunction and reduced NO bioavailability as central mechanisms promoting cardiomyocyte stiffness, interstitial fibrosis, and impaired ventricular relaxation. Recent clinical studies further suggest that glycocalyx degradation may represent an early event in HFpEF development. Increased circulating levels of glycocalyx-associated biomarkers, including perlecan and thrombomodulin, have been associated with features of diastolic dysfunction and adverse cardiovascular outcomes in patients with HFpEF [76]. Experimental and clinical data demonstrate reduced glycocalyx thickness, elevated circulating markers of shedding such as syndecan-1, and impaired mechanotransduction in patients with heart failure [77, 78].

Overall, EGX disruption in CVD involves the integration of multiple factors, including hemodynamic stress, inflammation, oxidative damage, and enzymatic degradation. Importantly, the glycocalyx acts not only as a marker of endothelial injury but also as an active regulator of disease progression, making it a potential therapeutic target in cardiovascular pathology.

Chronic psychological stress and PTSD are increasingly recognized as independent cardiovascular risk factors, characterized by persistent low-grade inflammation, oxidative stress, and endothelial dysfunction. Epidemiological studies demonstrate associations between PTSD and increased incidence of coronary artery disease, hypertension, arrhythmias, and adverse cardiovascular outcomes. These effects converge on sustained sympathetic activation, abnormal hypothalamic-pituitary-adrenal (HPA) axis activity, and immune dysfunction [60].

We propose that the EGX represents a critical interface linking stress-related neuroendocrine activation to vascular dysfunction. The glycocalyx is highly sensitive to catecholamines, inflammatory cytokines, and reactive oxygen species, all of which are elevated under chronic stress conditions. Stress-induced neurohumoral surges (e.g., norepinephrine, epinephrine), together with downstream inflammatory signaling, can activate proteases (MMPs, ADAMs) and glycosidases (heparanase, hyaluronidases), accelerating glycocalyx degradation and ectodomain shedding. This results in EGX thinning, vascular hyperpermeability, leukocyte adhesion, and microthrombosis – early events in atherogenesis and heart failure pathogenesis [12].

In addition to neuroendocrine and catecholamine-mediated mechanisms, persistent immune activation may further contribute to endothelial injury in PTSD [13]. Persistent immune activation is increasingly considered an important component of PTSD pathophysiology and may partially explain the elevated cardiovascular burden observed in affected individuals. Clinical studies have reported increased circulating levels of inflammatory mediators, including C-reactive protein, interleukin-6, and tumor necrosis factor-α, in patients with PTSD relative to control populations. These mediators are closely linked to endothelial dysfunction, oxidative stress, and progression of atherosclerotic processes, thereby providing a mechanistic connection between chronic psychological stress and CVD [79].

In addition to systemic cytokine imbalance, growing attention has been directed toward innate immune signaling pathways, particularly activation of the NLRP3 inflammasome complex. Experimental models of traumatic stress indicate that NLRP3-associated signaling may amplify inflammatory responses linked to both neural and vascular dysfunction [80].

Although direct experimental evidence in PTSD remains limited, studies in trauma and acute

stress conditions provide strong support for this hypothesis. Clinical and experimental data demonstrate that sympathoadrenal activation is closely associated with glycocalyx shedding and endothelial injury, as reflected by elevated circulating levels of syndecan-1 and impaired microvascular function [81, 82]. These findings indicate that catecholamine-driven and inflammatory pathways are sufficient to induce rapid EGX degradation and suggest that similar mechanisms may operate in chronic stress and PTSD.

In PTSD, persistent hyperarousal and sympathetic overdrive likely sustain a pro-shedding endothelial environment. Simultaneous changes in HPA axis activity, including dysregulated cortisol signaling, together with elevated pro-inflammatory cytokines, may further modulate endothelial glycosylation pathways [11]. These changes could alter HS sulfation patterns and hyaluronan turnover, thereby impairing barrier integrity and antithrombotic function. Such mechanisms are consistent with broader evidence of endothelial dysfunction and increased cardiovascular risk in PTSD populations [10, 83].

Beyond the vascular surface, chronic stress is also associated with systemic glycan remodeling. Immunoglobulin G (IgG) N-glycosylation profiles shift toward reduced galactosylation and sialylation with increasing inflammatory burden, enhancing pro-inflammatory effector functions. Large-scale population studies have established these glycan patterns as markers of biological aging, forming the basis of the "GlycanAge" concept [84]. These biomarkers are particularly relevant in stress biology, as glycan remodeling integrates neuroendocrine and inflammatory signals over longer time scales (weeks to months), complementing acute markers of glycocalyx shedding. Together, they provide a dual perspective on vascular injury: rapid EGX degradation reflecting acute endothelial stress, and gradual IgG glycan changes reflecting cumulative biological aging.

Previous studies have demonstrated an association between PTSD and altered IgG N-glycosylation profiles, supporting the concept of accelerated biological aging in individuals exposed to severe psychological trauma [85, 86]. Although exploratory, these findings support the hypothesis that trauma-related stress accelerates biological aging through immune glycan remodeling. When integrated with existing evidence linking PTSD to CVD, they suggest that GlycanAge, together with circulating EGX-derived biomarkers (e.g., syndecan-1, HA, HS), may provide a strategy for improved vascular risk stratification and monitoring of therapeutic responses.

Overall, PTSD and chronic emotional stress appear to converge on an integrated EGX–endothelium–immune glycan axis. Sustained neuroendocrine and inflammatory activation promotes glycocalyx degradation and endothelial dysfunction, while slower glycan remodeling reflects cumulative stress exposure. Together, these processes may contribute to the excess cardiovascular risk consistently observed in individuals with PTSD (Fig. 4).

In addition to chronic stress-related mechanisms, acute traumatic injury represents a major trigger of EGX disruption. Severe trauma, particularly when accompanied by hemorrhagic shock and ischemia-reperfusion, is associated with rapid and extensive glycocalyx degradation [1, 60]. This process is characterized by increased shedding of glycocalyx components, including syndecan-1 and HS, which correlates with injury severity, systemic inflammation, vascular hyperpermeability, and adverse clinical outcomes. Experimental and clinical evidence indicates that glycocalyx damage occurs early after trauma and contributes to microvascular dysfunction and coagulopathy. In critical illness and trauma settings, elevated circulating levels of glycocalyx-derived biomarkers are consistently associated with worse prognosis, supporting their role as indicators of endothelial injury and disease severity [87].

## 5. Therapeutic perspectives on EGX protection and restoration

Therapeutic strategies targeting the EGX are being considered for the treatment of vascular dysfunction and CVD. Interventions aimed at limiting glycocalyx degradation primarily focus on reducing inflammatory, oxidative, and mechanical stress [88]. Experimental evidence indicates that antioxidants, NO donors, and inhibitors of proteases and glycosidases can attenuate EGX shedding and preserve endothelial function [71].

Restorative approaches aim to reconstitute glycocalyx structure and function. Sulfated polysaccharides, HS mimetics, and HA-based therapies have demonstrated potential in preclinical models to restore barrier integrity, improve microvascular perfusion, and reduce leukocyte adhesion and vascular permeability [9].

Recent strategies also explore direct restoration of glycocalyx components. Experimental approaches include administration of HS mimetics,

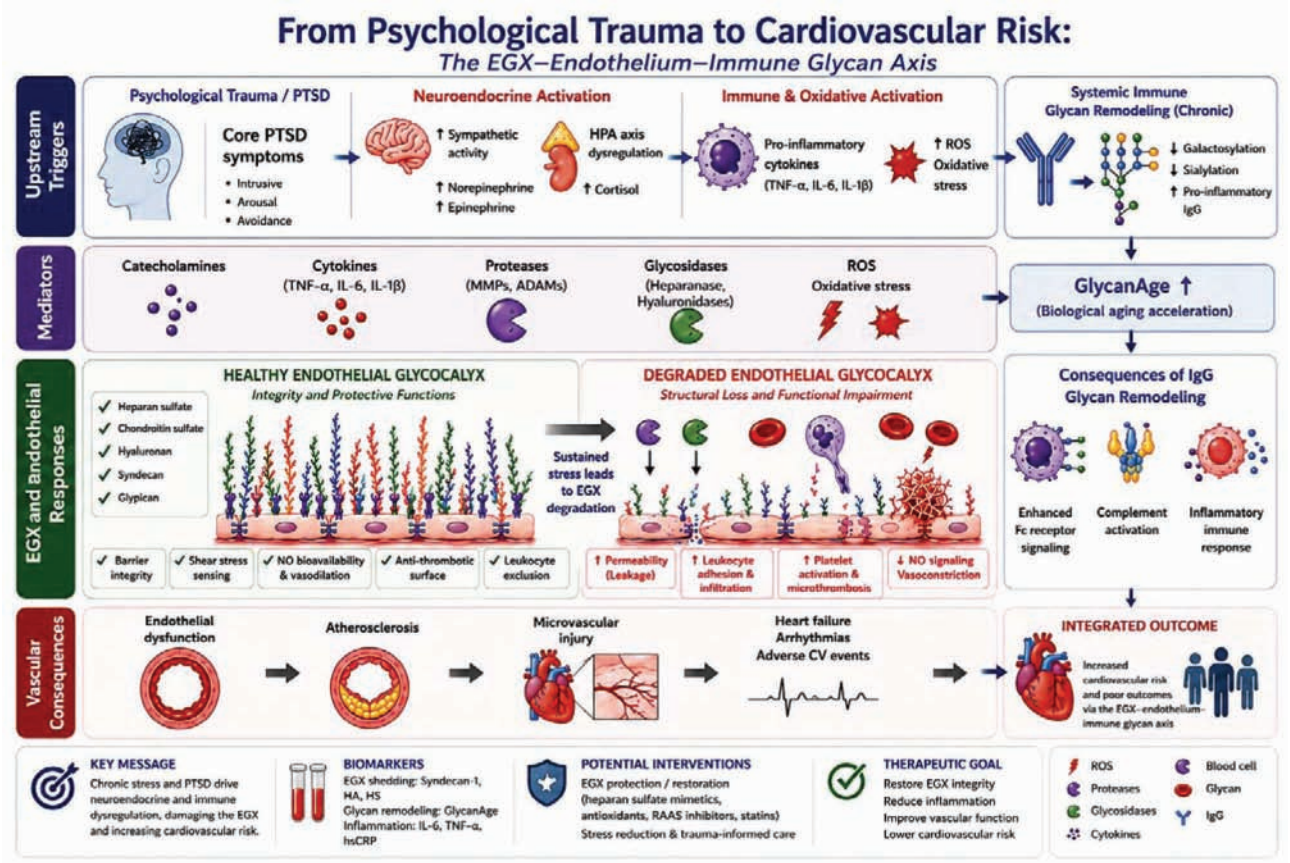


*Fig. 4. Stress-associated pathways leading to endothelial glycocalyx (EGX) degradation. Schematic representation of neuroendocrine and inflammatory pathways activated during chronic stress and PTSD, including catecholamine release, cytokine production, and oxidative stress. These signals promote protease- and glycosidase-mediated glycocalyx degradation, leading to endothelial dysfunction and increased cardiovascular risk, alongside systemic IgG glycan remodeling*

S1P analogues, and plasma-based therapies, which have been shown to stabilize the endothelial surface layer and reduce glycocalyx shedding. In addition, preliminary studies suggest that targeting proteoglycan turnover, including modulation of syndecan shedding or use of recombinant ectodomains, may represent a potential avenue for glycocalyx restoration, although these approaches remain at an early experimental stage [89].

Several pharmacological agents already used in clinical practice may influence EGX integrity indirectly through their endothelial-protective effects. Although most of these drugs were not originally designed as glycocalyx-targeted therapies, their ability to improve NO bioavailability, suppress inflammatory signaling, and modulate vascular permeability may contribute to preservation of the endothelial surface layer.

Among clinically relevant agents, sulodexide has the strongest direct association with glycocalyx protection [90]. As a glycosaminoglycan-based drug, sulodexide may support endothelial barrier function by promoting glycocalyx reconstruction, reducing vascular permeability, and attenuating inflammatory endothelial activation. In experimental models of sepsis-associated endothelial injury, sulodexide attenuated syndecan-1 shedding, restored glycocalyx integrity, reduced endothelial hyperpermeability, upregulated zonula occludens-1, and improved survival in septic animals. These effects were associated with modulation of NF-κB-dependent inflammatory signaling, supporting the concept that part of the vascular protective effects of sulodexide may be mediated through preservation and restoration of the EGX [91].

Other widely used cardiovascular drugs may also contribute to glycocalyx preservation through indirect mechanisms [92]. Statins exert pleiotropic endothelial effects beyond lipid lowering, including enhancement of eNOS-dependent NO production, attenuation of oxidative stress, and suppression of inflammatory signaling. Experimental and clinical studies have demonstrated that statins improve endothelial function, reduce expression of adhesion molecules, and attenuate vascular inflammation. These mechanisms are relevant to glycocalyx homeostasis, since oxidative stress, NF-κB activation, matrix metalloproteinases, and heparanase are recognized drivers of glycocalyx degradation and endothelial barrier dysfunction. Therefore, although direct evidence for statin-induced glycocalyx restoration remains limited, their anti-inflammatory and antioxidant endothelial effects may reduce the pathological conditions that promote glycocalyx shedding [8, 9].

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may have a more direct rationale in conditions associated with renin–angiotensin system activation. Excessive activation of the renin-angiotensin system is increasingly recognized as a contributor to endothelial dysfunction and microvascular injury. Angiotensin II promotes endothelial oxidative stress, inflammation, and impaired NO bioavailability, all of which contribute to glycocalyx damage. Experimental evidence from diabetic nephropathy models demonstrated that ACE inhibition with lisinopril attenuated glycocalyx loss and improved microvascular endothelial integrity, suggesting a protective effect on the endothelial surface layer under conditions of chronic metabolic injury [93]. These findings support the concept that inhibition of angiotensin II signaling may protect the microvascular glycocalyx, particularly in metabolic and inflammatory vascular injury.

L-arginine may be considered mainly as an indirect endothelial-supportive strategy rather than a specific glycocalyx-restoring agent. The rationale is based on its role as a substrate for eNOS. The EGX participates in shear stress mechanotransduction through heparan sulfate proteoglycans and glypican-1-dependent signaling pathways that regulate eNOS activation and NO production; therefore, impaired glycocalyx structure and reduced NO signaling are functionally interconnected [27-29,40]. However, direct evidence demonstrating restoration of glycocalyx structure by L-arginine remains limited, and its potential relevance should be interpreted through improvement of endothelial NO bioavailability and microvascular regulation.

Taken together, these findings support a shift toward targeting the glycocalyx as an upstream regulator of vascular health rather than exclusively focusing on downstream vascular complications. However, translation into clinical practice requires further investigation to establish efficacy, optimal timing, and long-term outcomes.

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# ЕНДОТЕЛІАЛЬНИЙ ГЛІКОКАЛІКС У НОРМІ ТА ПРИ ПАТОЛОГІЇ: МОЛЕКУЛЯРНІ МЕХАНІЗМИ І СТРЕС-АСОЦІЙОВАНЕ УШКОДЖЕННЯ СУДИН

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**Вступ.** Ендотеліальний глікокалікс – динамічний поверхневий шар ендотелію, який відіграє ключову роль у підтриманні бар'єрної функції судинної стінки, сприйнятті механічних сигналів із кровоплину, регуляції запалення, гемостазу та клітинної сигналізації. Складна молекулярна організація глікокаліксу зумовлює його високу чутливість до ензиматичної деградації, оксидативного стресу та дії медіаторів запалення, а його ушкодження є одним із ключових механізмів розвитку ендотеліальної дисфункції за різних патологічних станів. **Мета.** Узагальнити сучасні дані щодо будови ендотеліального глікокаліксу, біохімічних механізмів його деградації, ролі у розвитку серцево-судинних і стрес-асоційованих захворювань, а також перспективних терапевтичних підходів, спрямованих на захист і відновлення глікокаліксу. **Методи.** Огляд літератури виконано на основі аналізу 93 наукових публікацій, відібраних за результатами систематичного пошуку в десяти електронних базах даних. **Результати.** Аналіз літератури показав, що деградація глікокаліксу призводить до порушення ендотеліальної сигналізації за участю нітроген оксиду, підвищення судинної проникності, розвитку ендотеліального запалення та мікросудинної дисфункції у разі серцево-судинної патології. Сучасні дані також свідчать, що хронічний психоемоційний стрес і посттравматичний стресовий розлад можуть сприяти ушкодженню ендотеліального глікокаліксу через тривалу симпатичну активацію, оксидативний стрес і хронічне запалення низької інтенсивності. Окрім цього, розглянуто сучасні підходи, спрямовані на збереження та відновлення цілісності глікокаліксу, включаючи інгібування його ензимної деградації та стимуляцію процесів відновлення. **Висновки.** Отримані дані обґрунтовують доцільність спрямування терапевтичних підходів на збереження та відновлення ендотеліального глікокаліксу як ключового регулятора судинного гомеостазу, а не лише на корекцію наслідків судинного ушкодження.

Ключові слова: ендотеліальний глікокалікс, судинна проникність, деградація глікокаліксу, серцево-судинні захворювання, посттравматичний стресовий розлад.

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