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What every intensivist should know about the endothelial glycocalyx

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The endothelial glycocalyx is a complex, highly dynamic carbohydrate-rich layer lining the luminal surface of vascular endothelial cells. Historically described as a "fiber matrix" in early physiological studies [1], it is now recognized as a key regulator of microvascular function and systemic homeostasis. Rather than acting solely as a static physical barrier, current evidence highlights its active roles in mechanotransduction, modulation of autoregulation, and the maintenance of an anti-inflammatory and anticoagulant endothelial surface.

In the context of critical illness—including sepsis, trauma, and major surgery—glycocalyx degradation (shedding) is a hallmark feature that disrupts endothelial-leukocyte interactions and promotes inflammatory activation. This loss contributes to coagulation imbalance and organ dysfunction, particularly acute kidney injury (AKI). Furthermore, the integration of glycocalyx physiology into the revised Starling principle has fundamentally altered the conceptual framework of transvascular fluid exchange, leading to a paradigm shift in fluid therapy and resuscitation strategies [2] (See Fig. 1).

2.1. Is the endothelial glycocalyx merely a structural layer, or a key regulator of vascular homeostasis?

Functionally, the glycocalyx, together with endothelial junctions, acts as a key factor in regulating vascular permeability. Physiological studies conducted in frog mesenteric microvessels indicated that the glycocalyx, then described as the fiber matrix, played a role in regulating vascular barrier function, largely attributed to the presumed influence of serum albumin [3,4].

Direct measurements of vascular permeability indicate that even profound glycocalyx alterations, such as those observed during hemorrhagic shock and hemodilution, do not necessarily translate into increased transvascular permeability, challenging traditional assumptions regarding its barrier function [5,6]. Glycocalyx thickness and distribution, as well as endothelial cells, exhibit significant tissue-specific heterogeneity across different organ systems [7].

It plays a role in mechanotransduction, translating shear stress generated by blood flow into intracellular signals that regulate nitric oxide production and vascular tone. The glycocalyx also maintains an anticoagulant endothelial surface by binding antithrombin and limiting platelet adhesion [8]. Furthermore, it modulates inflammatory responses by preventing excessive leukocyte adhesion and migration. Through these mechanisms, the glycocalyx preserves microvascular integrity and homeostasis.

2.2. What's the importance of the endothelial glycocalyx in fluid dynamics?

2.2.1. *Reduction of friction*

The endothelial glycocalyx contributes to the reduction of friction between flowing blood and the vascular wall, thereby promoting more efficient and laminar blood flow [9].

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2.2.2. Vascular permeability

It acts as an endothelial gatekeeper that regulates the passage of macromolecules and cells from the bloodstream into surrounding tissues, influencing solute exchange and modulating inflammatory responses [10].

2.2.3. Mechanotransduction

The glycocalyx senses shear stress generated by blood flow and transduces these mechanical forces into intracellular signals, thereby influencing endothelial function and vascular homeostasis [11].

2.3. How to assess glycocalyx damage and shedding?

Glycocalyx shedding refers to the enzymatic degradation and loss of glycocalyx components into the circulation. This process, which involves stress on the endothelial surface and destabilization of the glycocalyx's cytoskeletal anchors, is often triggered by inflammatory cytokines, oxidative stress, and ischemia–reperfusion injury. Acute hyperglycemia and exposure to high levels of catecholamines further exacerbate glycocalyx disruption [12].

Significant glycocalyx degradation has been documented in sepsis, septic shock, trauma, burns, cardiac surgery, and acute respiratory distress syndrome [13]. Excessive intravenous fluid administration (fluid overload) has also been shown to contribute to glycocalyx injury, potentially creating a self-perpetuating cycle of capillary leak and edema.

2.3.1. Consequences of glycocalyx loss

Loss of glycocalyx integrity results in increased vascular permeability, leading to interstitial edema and impaired oxygen diffusion. The exposure of endothelial adhesion molecules promotes leukocyte and platelet adhesion, contributing to inflammation and microthrombosis. Collectively, these changes result in microcirculatory dysfunction and are strongly associated with organ failure and adverse outcomes in critically ill patients [14].

Advances in handheld vital microscopy (HVM) have improved bedside assessment of the microcirculation and leukocyte–endothelium interactions, although current optical resolution remains insufficient to directly visualize the thin glycocalyx layer itself. However, the observation of rolling and sticking leucocytes to the endothelial surface directly indicate the presence of glycocalyx shedding [15,16].

2.4. The revised Starling principle

The classical Starling equation described transvascular fluid exchange as a balance between hydrostatic and oncotic pressures across the capillary wall. However, this model failed to account for the presence and functional importance of the endothelial glycocalyx. The revised Starling principle correctly places the glycocalyx at the center of this regulation.

In the revised model, the effective oncotic pressure gradient exists between the plasma and the subglycocalyx space rather than the interstitium. The glycocalyx maintains a protein-poor subglycocalyx compartment, thereby limiting filtration under physiological conditions. Sustained capillary reabsorption is minimal, and excess interstitial fluid is primarily removed via the lymphatic system [2].

This paradigm shift has major implications for fluid management. It provides a mechanistic explanation for why aggressive fluid resuscitation leads to edema without sustained intravascular volume expansion, particularly when the glycocalyx is damaged. As a result, contemporary approaches increasingly favor restrictive, individualized fluid strategies over liberal resuscitation [17].

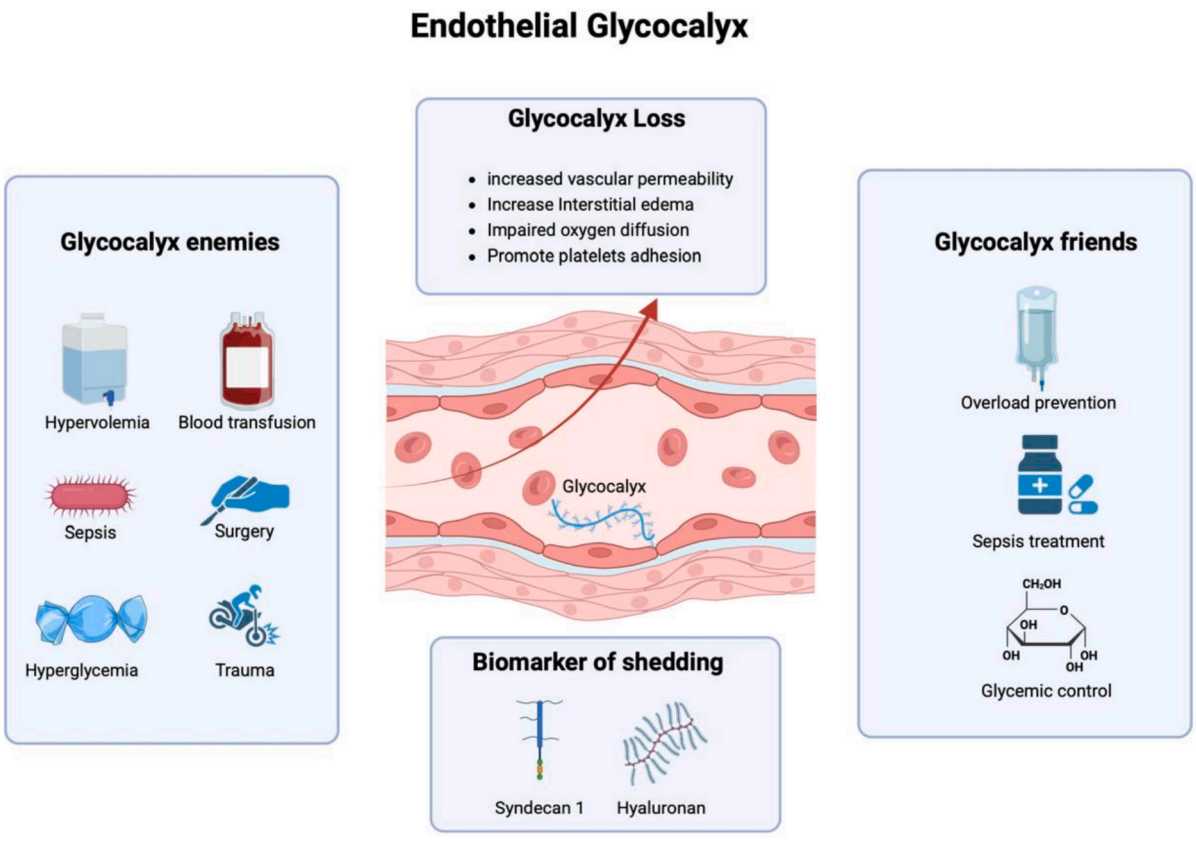

Fig. 1. Endothelial glycocalyx determinants of injury, consequences, and potential protective strategies.

2.5. Assessment of glycocalyx integrity

2.5.1. Circulating biomarkers

Several circulating biomarkers have been proposed as indirect measures of glycocalyx shedding, including syndecan-1, heparan sulfate, glycosaminoglycans, and hyaluronan. Elevated plasma levels of these components correlate with disease severity and mortality in sepsis, trauma, and cardiac surgery [18–20].

2.5.2. Microcirculatory imaging

Contemporary handheld vital microscopy (HVM) enables detailed assessment of microvascular blood flow at the bedside and, in newer versions, allow measurement of microcirculatory tissue hemoglobin saturation and indirect visualization of glycocalyx thickness by measuring the perfused boundary region. However, these technologies do not possess sufficient optical resolution to directly visualize the extremely thin glycocalyx layer (approximately 0.2 μm).

What is often reported as glycocalyx thickness is, in fact, derived from mathematical analysis of image-based parameters. While an increased perfused boundary region has been associated with adverse outcomes, it should be interpreted as an indirect surrogate marker rather than a direct visualization of glycocalyx structure [16,21].

2.5.3. Limitations

Despite growing interest, glycocalyx assessment remains largely confined to research settings. Available methods are indirect, technically demanding, and not yet standardized for routine clinical use [22].

2.6. Preventive strategies

Protecting and restoring the endothelial glycocalyx are key therapeutic goals in sepsis, as a healthy glycocalyx limits vasoconstriction, reduces tissue edema, and inhibits leukocyte and platelet adhesion. These actions directly attenuate inflammation, thrombosis, and tissue hypoxia. Strategies include avoidance of fluid overload, glycemic control, early and effective treatment of sepsis, and minimization of ischemia–reperfusion injury [17,23].

Future sepsis research should incorporate therapeutic approaches specifically designed to preserve and protect the endothelial glycocalyx. Albumin appears to stabilize the glycocalyx structure and preserve barrier function. Corticosteroids may reduce inflammatory shedding, while antithrombin, vitamin C, and sulodexide have demonstrated endothelial-protective properties in selected settings [17,24]. However, the evidence for these therapies remains heterogeneous, and to date, no treatment has been conclusively shown to regenerate the human glycocalyx.

2.7. Conclusion

The endothelial glycocalyx is a central regulator of vascular permeability, microcirculatory function, and fluid balance. Its degradation represents a unifying mechanism underlying edema formation and organ dysfunction in critical illness. Recognition of the glycocalyx has reshaped the understanding of transvascular fluid exchange and challenged traditional resuscitation strategies.

Future research should focus on standardized assessment methods and targeted therapies aimed at preserving or restoring glycocalyx integrity, with the potential to significantly improve outcomes in critically ill patients.

CRediT authorship contribution statement

Marcela de Almeida Lopes: Conceptualization, Writing – original draft. **Dimitri Gusmao-Flores:** Conceptualization, Writing – review & editing. **Can Ince:** Conceptualization, Writing – review & editing.

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Declaration of competing interest

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