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THE IMPORTANCE OF ALPHA–TUMOR NECROSIS FACTOR, SYNDECAN-1, AND HEPARAN SULFATE IN DIAGNOSING ENDOTHELIAL GLYCOCALYX DYSFUNCTION IN CHRONIC HEART FAILURE

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Introduction

Chronic heart failure (CHF) is a progressive clinical syndrome characterized not only by impaired cardiac pump function but also by multi-system vascular abnormalities, among which endothelial dysfunction plays a central role. Increasing evidence indicates that damage to the endothelial glycocalyx (EG)—a highly dynamic layer consisting of glycoproteins, proteoglycans, and glycosaminoglycans—is a key mechanism linking inflammation, microvascular impairment, and organ dysfunction in CHF.

Alpha–tumor necrosis factor (TNF-α) is a major pro-inflammatory cytokine initially identified in the 1970s as a product of activated macrophages. Subsequent research confirmed its production by endothelial and epithelial cells, smooth muscle cells, and cardiomyocytes, and highlighted its role in mediating systemic and vascular inflammatory responses [1]. Elevated TNF-α contributes to endothelial dysfunction through reduced nitric oxide (NO) bioavailability, cyclooxygenase-dependent vasoconstriction, and enhanced leukocyte adhesion.

Syndecan-1 and heparan sulfate, major structural constituents of the EG, are released into the bloodstream following glycocalyx shedding. Their circulating concentrations rise proportionally to the extent of endothelial damage and correlate with the severity of cardiovascular conditions, including CHF [2–4]. However, the diagnostic relevance, clinical correlates, and mechanistic validity of these biomarkers require systematic evaluation.

This review summarizes current evidence on the role of TNF-α, syndecan-1, and heparan sulfate as diagnostic and prognostic markers of glycocalyx dysfunction in chronic heart failure.

Methods

This article is a literature review. A structured search of PubMed, Scopus, and Web of Science was performed for publications between 2015 and 2025.

Inclusion and Exclusion Criteria

Included publications met the following criteria:

- Human or clinically relevant animal studies,
- Focus on endothelial glycocalyx, inflammation, or molecular mechanisms in CHF,
- Investigated TNF-α, syndecan-1, or heparan sulfate as biomarkers.

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Exclusion criteria:

- Non-cardiac primary diseases without vascular relevance,
- Articles lacking original data (unless providing essential mechanistic insight).

Data Extraction

Key findings were extracted, including:

- Mechanisms of biomarker elevation,
- Correlation with disease severity,
- Diagnostic and prognostic significance,
- Evidence of microscopic glycocalyx injury.

Main part.

TNF-α activates inflammatory gene transcription and promotes endothelial dysfunction by reducing NO bioavailability and inducing cyclooxygenase-mediated vasoconstrictive pathways [1]. Infusion studies in healthy humans demonstrated that TNF-α directly impairs vasodilation and increases vascular resistance, confirming its causal role in microvascular dysfunction.

Although early experimental data suggested that TNF-α blockade might provide therapeutic benefit, large clinical trials (RENEWAL and ATTACH) demonstrated increased mortality in CHF patients treated with anti-TNF agents. Etanercept treatment led to dramatic increases in circulating immunoreactive TNF-α, likely reflecting disruption of compensatory inflammatory pathways [1].

Syndecan-1 is released into the bloodstream during enzymatic cleavage of its extracellular domain. Elevated plasma syndecan-1 has repeatedly been associated with severity and prognosis in CHF. In a cohort of 201 patients hospitalized for acute decompensation, higher syndecan-1 levels predicted:

- Occurrence of acute kidney injury,
- Six-month mortality,
- Increased risk of death by 1.26-fold per 100 ng/mL increase [3].

A threshold of approximately 125 ng/mL demonstrated optimal prognostic discrimination. These findings indicate that syndecan-1 functions not only as a biochemical marker of EG degradation but as a clinically significant prognostic tool.

Heparan sulfate, a major EG glycosaminoglycan, is similarly released during glycocalyx degradation. Studies in ischemia-reperfusion injury and cardiac surgery demonstrated that rising HS levels directly parallel structural EG loss and recovery [5].

Bioinformatics research in dilated cardiomyopathy showed that HS-related gene expression correlates with fibrosis and immune activation, suggesting that HS is an active molecular participant in adverse myocardial remodeling rather than a passive vascular residue [6]. Large studies in heart failure with reduced ejection fraction confirmed that HS elevation is associated with increased complications and mortality [7].

Direct microscopic studies in animal hemorrhagic shock models demonstrated strong inverse correlations between circulating syndecan-1/HS concentrations and intravital imaging of

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EG thickness [4]. This provides mechanistic validation that elevated biomarkers reflect true structural glycocalyx degradation rather than non-specific inflammatory activation.

Multiple investigations show that pro-inflammatory pathways—especially TNF-α—upregulate matrix metalloproteinases and heparanase, accelerating enzymatic cleavage of syndecan-1 and HS from the endothelial surface [8]. Heparanase inhibition has been proposed as a promising strategy to preserve microvascular integrity [9].

Discussion

This review demonstrates that TNF-α, syndecan-1, and heparan sulfate constitute interconnected markers that capture the inflammatory and structural dimensions of endothelial glycocalyx dysfunction in CHF. TNF-α contributes to vessel wall injury through oxidative stress, impaired NO signaling, vascular inflammation, and enzyme activation. In turn, these pathways promote structural EG degradation, releasing syndecan-1 and HS into circulation.

Evidence across diverse clinical cohorts shows that:

- Syndecan-1 and HS correlate with heart failure severity, hospitalization rates, and survival,
- Elevated TNF-α provides mechanistic linkage between inflammatory activation and EG breakdown,
- Biomarker levels reflect true microscopic injury confirmed by intravital imaging.

These biomarkers enable:

1. Early detection of endothelial injury,
2. Enhanced prognostic accuracy,
3. Monitoring of treatment response,
4. Potential stratification of patients who may benefit from therapies targeting inflammation or glycocalyx protection.

Importantly, anti-TNF strategies have failed in CHF, likely because global cytokine blockade disrupts both harmful and compensatory pathways. This highlights the need for selectively targeted therapies—such as heparanase inhibition or agents restoring EG integrity.

Future research should:

- Establish predictive cut-off values for different CHF phenotypes,
- Conduct longitudinal monitoring to assess therapeutic reversibility of EG injury,
- Explore biomarker panels combining syndecan-1, HS, hyaluronan, and inflammatory mediators.

Conclusion

TNF-α, syndecan-1, and heparan sulfate are robust and clinically meaningful markers of endothelial glycocalyx degradation in chronic heart failure. Their measurement offers mechanistic insight into vascular injury, strong prognostic value, and potential utility for treatment monitoring and personalized risk stratification. Integrating these biomarkers into clinical practice may enhance the diagnostic accuracy and management of CHF.

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