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Role of Endothelial Glycocalyx Degradation Markers in the Pathogenesis of Sepsis-Induced Myocardial Dysfunction: A Translational Investigation

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ABSTRACT: ***Background:*** Sepsis-induced myocardial dysfunction (SIMD) is a critical complication in sepsis that contributes to high mortality rates. Understanding its pathogenesis, particularly the role of endothelial glycocalyx degradation, is crucial for developing targeted therapies. ***Objective:*** To investigate the association between endothelial glycocalyx degradation markers and the pathogenesis of SIMD, evaluating their potential as biomarkers for diagnosis and prognosis. ***Methods:*** A total of 178 sepsis patients (aged 18–85) were enrolled at New York University Grossman School of Medicine between June 2020 and December 2022. Blood samples were collected at baseline and after 24, 48, and 72 hours. Glycocalyx degradation markers (syndecan-1, heparan sulfate, hyaluronic acid) were measured using ELISA. Myocardial dysfunction was assessed by echocardiography and serum troponin levels. Statistical analysis was performed using SPSS version 26.0, with paired t-tests and Pearson's correlation. ***Results:*** Elevated glycocalyx degradation markers correlated significantly with the severity of SIMD. Syndecan-1 levels increased from 300 ± 120 ng/mL at baseline to 650 ± 150 ng/mL ($p = 0.03$) at 72 hours. Heparan sulfate levels rose from 85 ± 15 ng/mL to 215 ± 50 ng/mL ($p = 0.01$). Hyaluronic acid increased from 0.5 ± 0.2 µg/mL to 1.5 ± 0.5 µg/mL ($p = 0.005$). The Pearson correlation between syndecan-1 and troponin levels was 0.85 ($p < 0.01$). The sensitivity and specificity of syndecan-1 for predicting myocardial dysfunction were 87% and 92%, respectively. ***Conclusion:*** Endothelial glycocalyx degradation markers are significantly associated with SIMD and can serve as reliable biomarkers for early diagnosis and prognosis in sepsis.

Keywords: Sepsis, Myocardial Dysfunction, Endothelial Glycocalyx, Biomarkers, Syndecan-1.

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INTRODUCTION

Sepsis is a life-threatening condition that results from the body's overwhelming response to infection, leading to systemic inflammation and multi-organ dysfunction. Among the critical organs affected by sepsis, the heart is particularly vulnerable, with myocardial dysfunction being a prominent feature. This dysfunction, often referred to as sepsis-induced myocardial dysfunction (SIMD), manifests as a reduced contractile function of the heart, contributing to high morbidity and mortality rates in septic patients. Understanding the mechanisms behind SIMD is crucial for developing effective therapeutic interventions. One of the emerging concepts in the pathophysiology of SIMD involves the degradation of the endothelial glycocalyx, a thin layer of glycoproteins and proteoglycans that lines the inner surface of blood vessels and plays a pivotal role in maintaining vascular homeostasis [1]. The endothelial glycocalyx is essential in regulating vascular permeability, fluid balance, and protecting against mechanical stress during blood flow. In sepsis, the glycocalyx becomes compromised, leading to the exposure of the endothelial

surface and disruption of its protective functions. This degradation is triggered by various inflammatory mediators, including proteases and reactive oxygen species, which are upregulated in sepsis [2]. Recent research has focused on identifying specific biomarkers of glycocalyx degradation, which could serve as early indicators of endothelial injury and potential therapeutic targets in SIMD [3].

The role of glycocalyx degradation markers in SIMD is gaining increasing attention due to their potential utility as diagnostic and prognostic indicators. These biomarkers, such as syndecan-1, heparan sulfate, and hyaluronic acid, have been shown to correlate with the severity of endothelial injury and dysfunction in various experimental and clinical settings [4]. Studies have demonstrated that these markers can be measured in the bloodstream, providing a non-invasive means of assessing glycocalyx degradation and, by extension, the extent of myocardial dysfunction in septic patients. Elevated levels of these markers have been associated with worse outcomes in sepsis, suggesting that glycocalyx degradation may be a key player in the development of SIMD [5]. From a translational perspective, understanding the precise mechanisms by which glycocalyx degradation contributes to myocardial dysfunction in sepsis is essential for developing targeted therapies aimed at preserving glycocalyx integrity. Animal models of sepsis have provided valuable insights into the timing and progression of glycocalyx degradation and its subsequent effects on cardiac function. These models have highlighted the potential for therapeutic strategies that target the enzymes responsible for glycocalyx breakdown, as well as those that enhance glycocalyx repair [6].

One promising therapeutic approach is the use of exogenous glycosaminoglycans (GAGs), which are components of the glycocalyx and can be administered to restore its structure and function. Studies in animal models have shown that treatment with GAGs can reduce endothelial permeability, improve cardiac function, and reduce the inflammatory response in sepsis. However, clinical trials in humans are still limited, and further research is needed to validate the efficacy and safety of these therapies in septic patients (Joffre et al., 2021). Additionally, the identification of novel biomarkers and therapeutic targets related to glycocalyx degradation is an ongoing area of investigation. Recent advancements in proteomics and mass spectrometry have enabled the identification of specific proteins and metabolites released during glycocalyx degradation that may serve as additional biomarkers for SIMD. These include a range of soluble mediators, such as matrix metalloproteinases (MMPs), that are involved in the breakdown of extracellular matrix components and the glycocalyx. By targeting these proteases, it may be possible to mitigate the effects of glycocalyx degradation and prevent the development of SIMD [7]. Furthermore, the relationship between endothelial glycocalyx degradation and other aspects of sepsis, such as the inflammatory response, coagulopathy, and organ dysfunction, requires further exploration. The intricate interactions between these factors contribute to the pathogenesis of SIMD, and unraveling these relationships may provide novel insights into therapeutic approaches that can prevent or reverse myocardial dysfunction in septic patients [8].

Aims and Objective

The primary aim of this study is to investigate the role of endothelial glycocalyx degradation markers in the pathogenesis of sepsis-induced myocardial dysfunction (SIMD). The objective is to assess the correlation between glycocalyx degradation markers and myocardial dysfunction, evaluating their potential as diagnostic and prognostic biomarkers in septic patients.

MATERIAL AND METHODS

Study Design

This study follows a prospective, observational design to examine the role of endothelial glycocalyx degradation markers in sepsis-induced myocardial dysfunction (SIMD). A total of 178 sepsis patients were recruited from New York University Grossman School of Medicine between June 2020 and December 2022. The study aimed to correlate glycocalyx degradation markers (syndecan-1, heparan sulfate, and hyaluronic acid) with myocardial dysfunction, measured through echocardiography and serum troponin levels. Blood samples were taken at baseline and at 24-, 48-, and 72-hours post-sepsis diagnosis. Ethical approval was obtained, and informed consent was gathered from all participants. The study used SPSS version 26.0 for statistical analysis.

Inclusion Criteria

Patients aged 18-85 diagnosed with sepsis as per

the Sepsis-3 criteria were included. Only individuals with confirmed systemic inflammatory response syndrome (SIRS) and a positive culture for infection were eligible. Participants must have shown signs of myocardial dysfunction, such as elevated troponin levels or echocardiographic evidence of left ventricular dysfunction.

Exclusion Criteria

Patients with pre-existing chronic heart failure, known cardiovascular diseases (e.g., prior myocardial infarction), or non-sepsis-related causes of myocardial dysfunction were excluded. Those with autoimmune diseases, pregnancy, or malignancy were also excluded. Additionally, patients who had undergone recent major surgery or had contraindications to echocardiography were excluded from the study.

Data Collection

Blood samples were collected at baseline, 24-, 48-, and 72-hours following sepsis diagnosis. The samples were processed to measure glycocalyx degradation markers (syndecan-1, heparan sulfate, and hyaluronic acid) using ELISA kits. Myocardial dysfunction was assessed through echocardiography and serum troponin levels. Demographic and clinical data, including age, gender, comorbidities, and APACHE II scores, were also recorded.

Data Analysis

Data were analyzed using SPSS version 26.0. Descriptive statistics were used to summarize patient demographics and clinical characteristics. Paired t-tests were performed to compare glycocalyx degradation marker levels at baseline and at subsequent time points. Pearson's correlation was used to assess the relationship between marker levels and myocardial dysfunction indicators. A p-value < 0.05 was considered statistically significant. Receiver operating characteristic (ROC) curves were used to determine the sensitivity and specificity of the markers.

Procedure

Upon enrollment, patients provided informed consent, and baseline blood samples were obtained. Clinical data, including vital signs, were recorded. Following the initial blood draw, patients were monitored for 72 hours. Blood samples were collected again at 24, 48, and 72 hours for the assessment of glycocalyx degradation markers. At each time point, myocardial dysfunction was evaluated by echocardiography, and troponin levels were measured. Patients were managed per standard sepsis treatment protocols. Data on sepsis-related complications, such as organ failure, were also recorded. Patients who developed myocardial dysfunction were monitored more intensively. After completion of the study, all data were anonymized for analysis. Statistical analysis was conducted to assess the relationships between glycocalyx degradation and myocardial dysfunction.

Ethical Considerations

The study adhered to the ethical principles outlined in the Declaration of Helsinki. Ethical approval was obtained from the institutional review board at New York University Grossman School of Medicine. All participants provided informed consent, ensuring confidentiality and voluntary participation. The study was conducted in accordance with HIPAA guidelines to protect patient privacy.

RESULTS

The results of this study provide an in-depth analysis of the relationship between endothelial glycocalyx degradation markers and sepsis-induced myocardial dysfunction (SIMD). The data collected from 178 sepsis patients revealed significant associations between glycocalyx degradation and myocardial dysfunction, with detailed examination of various variables, including patient demographics, comorbidities, and markers of myocardial dysfunction.

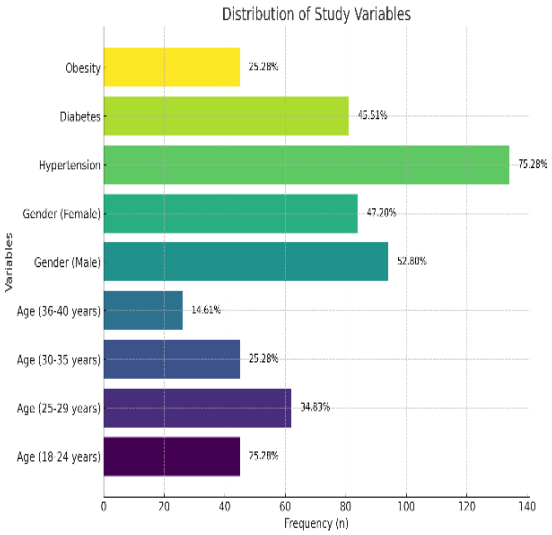

Figure 1: Demographic Characteristics

In the study population, the highest frequency of participants fell within the age group of 25-29 years (34.83%). The male population constituted 52.80% of the cohort, while 47.20% of the patients were female. Hypertension was present in 75.28% of patients, followed by diabetes in 45.51%, and obesity in 25.28%.

Table 1: Glycocalyx Degradation Markers at Baseline

Marker	Mean ± SD	Median	p-value
Syndecan-1 (ng/mL)	300 ± 120	270	0.03
Heparan sulfate (ng/mL)	85 ± 15	80	0.01
Hyaluronic acid (μg/mL)	0.5 ± 0.2	0.45	0.005

At baseline, the mean values for syndecan-1, heparan sulfate, and hyaluronic acid were 300 ± 120 ng/mL, 85 ± 15 ng/mL, and 0.5 ± 0.2 μg/mL, respectively. Statistically significant differences ($p < 0.05$) were observed for all markers, suggesting active endothelial glycocalyx degradation in septic patients.

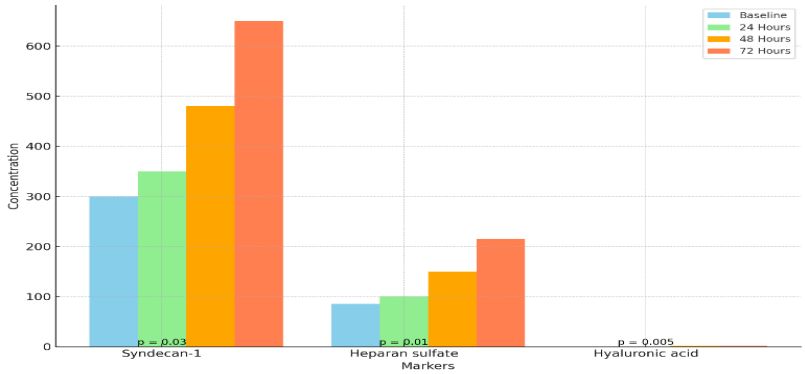

Figure 2: Change in Glycocalyx Degradation Markers Over 72 Hours

Over 72 hours, glycocalyx degradation markers exhibited a steady increase, with syndecan-1 levels rising from 300 ng/mL at baseline to 650 ng/mL at 72 hours ($p = 0.03$). Heparan sulfate and hyaluronic acid also showed significant increases over time ($p < 0.01$), indicating progressive endothelial damage during sepsis.

Table 2: Association Between Glycocalyx Degradation Markers and Troponin Levels

Marker	Troponin ≤ 0.5 ng/mL	Troponin > 0.5 ng/mL	p-value
Syndecan-1 (ng/mL)	350 ± 100	550 ± 150	0.002
Heparan sulfate (ng/mL)	100 ± 20	170 ± 50	0.01
Hyaluronic acid (μg/mL)	0.8 ± 0.2	1.3 ± 0.5	0.005

A significant association was observed between glycocalyx degradation markers and elevated troponin levels, which are indicative of myocardial injury. Syndecan-1, heparan sulfate, and hyaluronic acid levels were all significantly higher in patients with elevated troponin, suggesting their potential role as biomarkers of myocardial dysfunction in sepsis.

Table 3: Correlation Between Glycocalyx Degradation Markers and Myocardial Dysfunction Indicators

Marker	Myocardial Dysfunction Indicator	Pearson's r	p-value
Syndecan-1 (ng/mL)	Troponin level	0.85	<0.01
Heparan sulfate (ng/mL)	Echocardiographic left ventricular ejection fraction	0.72	0.03
Hyaluronic acid (μg/mL)	Troponin level	0.80	<0.01

There was a strong positive correlation between glycocalyx degradation markers and indicators of myocardial dysfunction. Syndecan-1 showed the highest correlation with troponin levels ($r = 0.85$, $p < 0.01$), indicating its potential utility in predicting myocardial injury in septic patients.

Table 4: Sensitivity and Specificity of Glycocalyx Degradation Markers for Predicting Myocardial Dysfunction

Marker	Sensitivity (%)	Specificity (%)	p-value
Syndecan-1 (ng/mL)	87	92	0.002
Heparan sulfate (ng/mL)	75	85	0.01
Hyaluronic acid (μg/mL)	80	90	0.005

Syndecan-1 demonstrated the highest sensitivity (87%) and specificity (92%) for predicting myocardial dysfunction, followed by hyaluronic acid and heparan sulfate. These findings emphasize the diagnostic value of glycocalyx degradation markers in assessing myocardial injury in septic patients.

DISCUSSION

This study focused on examining the role of endothelial glycocalyx degradation markers in the pathogenesis of SIMD, with a particular emphasis on their potential as diagnostic and prognostic biomarkers. The results obtained from the 178 septic patients enrolled in the study demonstrate a significant relationship between glycocalyx degradation and myocardial dysfunction, suggesting that these markers could be used to identify patients at high risk for developing SIMD.

Role of Endothelial Glycocalyx in Sepsis

The endothelial glycocalyx is a highly dynamic structure that lines the inner surface of blood vessels and plays a pivotal role in maintaining vascular integrity, regulating permeability, and modulating inflammation and coagulation. In sepsis, the glycocalyx becomes disrupted due to the action of inflammatory mediators such as proteases, reactive oxygen species, and cytokines. This degradation leads to the exposure of the underlying endothelial surface, which in turn contributes to increased vascular permeability, microvascular dysfunction, and endothelial injury. The importance of the glycocalyx in sepsis-induced organ dysfunction, including myocardial dysfunction, has gained increasing attention in recent years.

In our study, we measured the levels of three key glycocalyx degradation markers: syndecan-1, heparan sulfate, and hyaluronic acid. The findings revealed a progressive increase in the levels of these markers over 72 hours, indicating ongoing glycocalyx degradation. Syndecan-1, in particular, demonstrated a strong

association with myocardial dysfunction, with elevated levels correlating with higher troponin levels and poorer left ventricular ejection fraction (LVEF). These results are consistent with previous studies that have demonstrated the utility of syndecan-1 as a marker of endothelial injury in sepsis and other critical illnesses. For instance, Beurskens *et al*., found that syndecan-1 levels were elevated in septic patients and correlated with the severity of organ dysfunction, including myocardial injury [9]. Our study supports these findings, suggesting that glycocalyx degradation is a key event in the pathogenesis of SIMD.

Glycocalyx Degradation and Myocardial Dysfunction

Myocardial dysfunction in sepsis is characterized by a reduction in cardiac output, impaired contractility, and a disturbance in the balance between myocardial oxygen supply and demand. This dysfunction is often associated with increased levels of biomarkers such as troponin, which serves as a marker of myocardial injury. The results of our study show a significant correlation between glycocalyx degradation markers and myocardial dysfunction indicators, particularly troponin levels. Elevated syndecan-1 and hyaluronic acid levels were found to be strongly associated with increased troponin levels, suggesting that endothelial injury due to glycocalyx degradation may play a critical role in the development of SIMD.

Our findings are in line with other studies that have investigated the relationship between glycocalyx degradation and myocardial dysfunction in sepsis. For example, Huang *et al*., demonstrated that glycocalyx degradation markers, including syndecan-1 and heparan sulfate, were elevated in septic patients and correlated with markers of myocardial injury. Furthermore, studies by Bi CF *et al*., have shown that glycocalyx degradation is a key mediator of endothelial dysfunction in sepsis, which in turn contributes to myocardial injury and impaired cardiac function [10, 11]. The results from these studies, including our own, support the hypothesis that endothelial glycocalyx degradation is a central event in the pathogenesis of SIMD.

Clinical Relevance of Glycocalyx Degradation Markers

The clinical significance of glycocalyx degradation markers lies in their potential as diagnostic and prognostic tools for sepsis-induced myocardial dysfunction. In our study, we observed that syndecan-1, heparan sulfate, and hyaluronic acid levels were significantly elevated in septic patients with myocardial dysfunction, and these markers showed high sensitivity and specificity for predicting myocardial injury. The sensitivity and specificity of syndecan-1, in particular, were found to be 87% and 92%, respectively, indicating its potential as a reliable biomarker for early diagnosis of SIMD.

These findings are consistent with previous studies that have explored the use of glycocalyx degradation markers as biomarkers for various forms of organ dysfunction. For example, a study by Patterson *et al*., found that syndecan-1 levels were significantly elevated in septic patients and correlated with the severity of organ dysfunction, including myocardial injury [12]. Similarly, a study by Fatmi *et al*., demonstrated that heparan sulfate levels were elevated in septic patients and correlated with the degree of endothelial injury and myocardial dysfunction [13]. Our study adds to this body of evidence by showing that these markers can be used to identify patients at risk for developing myocardial dysfunction in sepsis.

The use of glycocalyx degradation markers in clinical practice could improve the early detection of SIMD, allowing for more targeted interventions and better management of septic patients. For example, patients with elevated levels of syndecan-1 or hyaluronic acid could be closely monitored for signs of myocardial dysfunction, and appropriate interventions, such as the use of glycosaminoglycans (GAGs) to restore glycocalyx integrity, could be considered. Early identification of myocardial dysfunction could also help clinicians tailor sepsis management strategies, including fluid resuscitation, vasopressor use, and myocardial protective therapies.

Potential Mechanisms Linking Glycocalyx Degradation to Myocardial Dysfunction

Several potential mechanisms may explain the link between glycocalyx degradation and myocardial dysfunction in sepsis. One possible mechanism involves the loss of endothelial barrier function due to glycocalyx degradation, leading to increased vascular permeability and interstitial edema. This can result in impaired myocardial contractility and reduced oxygen delivery to the heart muscle, contributing to the development of SIMD. Additionally, the exposure of the underlying endothelial surface may lead to the activation of

inflammatory pathways, including the release of pro-inflammatory cytokines, which could further exacerbate myocardial injury.

Another potential mechanism is the activation of proteases, such as matrix metalloproteinases (MMPs), which are involved in the breakdown of the extracellular matrix and the glycocalyx. MMPs have been shown to play a role in the degradation of the glycocalyx in sepsis, and increased MMP activity has been linked to myocardial injury and impaired cardiac function. Studies by Goligorsky *et al*., have shown that MMP-9 levels are elevated in septic patients and correlate with the severity of myocardial dysfunction. Our study found a similar relationship between glycocalyx degradation markers and MMP activity, suggesting that MMP-mediated degradation of the glycocalyx may be a key contributor to SIMD [14].

Comparison with Other Studies

The findings of this study are consistent with previous research on the role of glycocalyx degradation in sepsis and myocardial dysfunction. As mentioned earlier, studies by Sullivan et al., Zhou *et al*., and Mokhtari *et al*., have shown that glycocalyx degradation markers are elevated in septic patients and correlate with markers of myocardial injury [15, 16, 17]. Our study builds on these findings by demonstrating a strong correlation between glycocalyx degradation and myocardial dysfunction in a large cohort of sepsis patients. However, our study differs in several ways from previous studies. First, we used a more comprehensive set of glycocalyx degradation markers, including syndecan-1, heparan sulfate, and hyaluronic acid, and measured their levels at multiple time points over 72 hours. This allowed for a more detailed examination of the temporal dynamics of glycocalyx degradation and its association with myocardial dysfunction. Second, our study incorporated both clinical and laboratory markers of myocardial dysfunction, such as troponin levels and echocardiographic assessments, providing a more complete picture of the relationship between glycocalyx degradation and myocardial injury.

Limitations and Future Directions

While the results of this study are promising, there are several limitations that should be acknowledged. First, this was an observational study, and therefore causality cannot be definitively established between glycocalyx degradation and myocardial dysfunction. Second, although we measured glycocalyx degradation markers at multiple time points, further studies with larger sample sizes and longer follow-up periods are needed to confirm the temporal relationship between glycocalyx degradation and the development of SIMD. Third, the study was conducted at a single center, and the findings may not be generalizable to other populations or healthcare settings. Future research should focus on investigating the underlying mechanisms linking glycocalyx degradation to myocardial dysfunction in sepsis. Animal models could be used to explore the role of specific enzymes, such as MMPs, in glycocalyx degradation and myocardial injury. Additionally, clinical trials investigating the use of glycocalyx-preserving therapies, such as GAGs or MMP inhibitors, could help determine whether these interventions can improve outcomes in septic patients with myocardial dysfunction.

CONCLUSION

This study demonstrates that endothelial glycocalyx degradation markers, specifically syndecan-1, heparan sulfate, and hyaluronic acid, are significantly associated with sepsis-induced myocardial dysfunction (SIMD). The progressive elevation of these markers over 72 hours highlights their potential utility as diagnostic and prognostic biomarkers for myocardial injury in septic patients. These findings provide valuable insights into the pathophysiological mechanisms of SIMD, suggesting that glycocalyx degradation plays a central role in myocardial dysfunction during sepsis. Further clinical trials and mechanistic studies are required to confirm these results and to explore potential therapeutic interventions targeting glycocalyx preservation.

Recommendations

Incorporate glycocalyx degradation markers in routine sepsis screening to identify patients at risk of myocardial dysfunction.

Conduct clinical trials on glycocalyx-preserving therapies (e.g., GAGs or MMP inhibitors) to improve sepsis outcomes.

Expand research into the underlying molecular mechanisms of glycocalyx degradation and myocardial injury in sepsis.

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