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A comprehensive review of glycocalyx investigation and therapeutic applications in sepsis and septic shock

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ABSTRACT

Background: Sepsis is a global health challenge that causes more than 11 million deaths annually and represents a substantial medical and economic burden. With rising treatment costs and significant mortality rates associated with organ dysfunction and septic shock, research efforts have focused on investigating the mechanism of glycocalyx (GCX) degradation as well as its regenerative capacity. Therefore, GCX has become a target in therapeutic strategies.

Methods: We performed a comprehensive review of articles published in PubMed database between 2014 and 2024, in the English language, dealing with statistical data, morphological and physiological aspects of the GCX, pathophysiological mechanisms, in vivo and in vitro research methods, clinical and laboratory experiences, therapeutic strategies, and innovative methods of prevention, both in the context of sepsis and its associated complications.

Results: The database search identified 300 records on the topic. After title/abstract screening, 187 articles were assessed in full text for eligibility, including articles with additional topics addressing the main topic. Of these, a total of 70 studies were included.

Conclusions: Exploring the structure of GCX holds real potential in the diagnosis and treatment of sepsis and its complications. Current research focuses on understanding GCX degradation, correlating its components with sepsis severity, predicting disease progression, and evaluating the impact of therapeutic strategies on GCX components.

Keywords: endothelial cell, glycocalyx, inflammation, sepsis, septic shock

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INTRODUCTION

Sepsis, according to the latest statistical data, has an incidence of approximately 48.9 million worldwide and is the cause of more than 11.0 million deaths, representing 19.7% of all global deaths [1]. The average cost of treatment for a single patient is estimated to be around €16,000, the cost of intensive care unit care exceeds €27,000 per patient, and severe sequelae can increase treatment and care costs [2]. Treatment of sepsis is possible, and prompt and correctly targeted interventions improve the prognosis.

The stormy development of the medical clinical branches has created the need to define and clinically stage the damage produced to the glycocalyx (GCX) by the inflammatory mediators released by the immune system. Sepsis occurs as a result of impaired immune system function, and is manifested by a host hyper responsiveness to infection, which can be clinically evident. Thus, sepsis damages one's own tissues and organs, endangering life [3]. Sequential organ failure assessment score (SOFA) [4], cardiovascular score in the first 24 hours after admission [5] and serum GCX components [6] are the basic criteria for determining the severity of sepsis in the clinic. If the SOFA score increases by 2 points or more, it is an organ dysfunction [4]. Septic shock represents severe sepsis associated with persistent organ dysfunction and marked hypotension that does not respond to volume repletion and the presence of metabolic acidosis [7]. According to statistics, an organ dysfunction is fatal in

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approximately 24.4% of patients and in the case of septic shock leads to death in 34.7% of cases within 30 days [8].

At present, the main research objectives are elucidating the mechanism of degradation of GCX, correlating elevated levels of its components in plasma and urine with the severity of patients, predicting the course of sepsis, evaluating the benefits and harms of using fluid therapy during sepsis and modifying the components of the GCX under its action [9].

THE COMPONENTS AND STRUCTURE OF GLYCOCALIX

GCX is a negatively charged carbohydrate layer that coats the inner side of the endothelial cells (ECs) membrane like a gel. From a biochemical point of view, it consists of basic proteins – glypicans and syndecans (SDCs) from the class of proteoglycans (PGs) [10], which present primary selectivity for plasma macromolecules; glycosaminoglycans (GAGs) sulfated (heparan (HS), chondroitin (CS), heparin (Hep)) or non-sulfated (hyaluronic acid (HA) and chondroitin acid (CA)) covalently attached to PGs in the form of chains, which can be from 2 to 4 chains; CD44 receptors for HA and several other ligands such as collagens and matrix metalloproteinases (MMPs); associated plasma proteins (albumin and antithrombin), which together with GAGs expand into the lumen of the vessel, contributing to the continuous movement of blood cells and restricting the access of inflammatory cells to the endothelial surface [11].

There are many types of PGs and GAGs, but the components of GCX with diagnostic value in sepsis are: SDC of 4 types (PG); HA (uncharged GAG) – hydrophilic component, which ensures the gelled consistency of the GCX due to water retention, being attached to the CD44 glycoprotein or to other sulfated GAGs, with which it forms complexes. HS and CS (negatively charged GAGs) have the same diagnostic utility – they interact electrostatically with albumin, fibrinogen, and fibronectin, and also interact with chemokines, integrins and selectins, consequently participating during inflammation in modulating the recruitment, adhesion and transmigration of leukocytes [12].

Due to its gelatinous structure and orientation within the vascular lumen, GCX plays the role of: barrier in reducing the passage of water and colloids [13], especially the entry of sodium into ECs (hypernatremia damages the GCX) [14], structural determinant of the oncotic gradient that opposes vascular permeability and limits the transvascular movement of negatively charged molecules and greater than 70 kDa [9]; protection – produces nitric oxide, protects ECs from oxidative stress by dilating blood vessels and reducing leukocyte and platelet adhesion [15]; regulation of homeostasis, vascular system permeability, coagulation and adhesion processes on the surface of ECs [16]; regulation of transvascular fluid flow and microvascular tone by means of the frictional forces of the fluid that the GCX senses and transmits to the ECs, initiating vasorelaxation [9].

Inflammatory mechanisms are represented by the direct cleavage of SDC under the action of MMPs, HS chains attached to basic PGs by hyaluronidases (Hyals) and heparanases (HPSEs), and HA by Hyals, thrombin, elastase, plasminogen or cathepsin B [9].

A primary role in causing the septic process belongs to the endotoxin of enterobacteria – lipopolysaccharide (LPS) and the interaction with its binding protein (LBP). The formed complex attaches to the protein receptor complex, and the triggered signaling cascade results in the secretion of cytokines, which destroy the junctions between cells and as a consequence degrade the GCX [17]. This inflammatory process can occur through both intracellular and extracellular pathways [18]. The administration of LPS eliminates the ectodomain CD44 both in vivo and in vitro, under the action of sheddase MMP15 (ADAM15) – a membrane-bound enzyme that cleaves extracellular portions of transmembrane proteins and releases soluble ectodomains on the cell surface. It has also been observed that in ECs with inhibited MMP15 sheddase, LPS-induced CD44 cleavage was significantly reduced, while MMP15 sheddase overexpression resulted in LPS response and CD44 cleavage [19]. Experimental administration of LPS demonstrated a significant reduction in GCX thickness, both when administered intravenously in the mouse aorta model and in the case of in vitro treatment of the human umbilical vein endothelial cells (HUVEC) [20].

In the context of GCX, which ensures the structural and functional integrity of the microcirculation, and the septic process, which damages the vascular barrier through proinflammatory cytokines, the role of acute and chronic hyperglycemia was evaluated. The elaborated hypothesis aims at the fact that elevated blood glucose levels favor vascular inflammation and catalyze the activation of GCX-degrading enzymes, constituting an additional factor of endothelial dysfunction. GCX integrity was established based on its thickness and removed components in an experimental model using HUVECs placed in microfluidic devices (MFDs) to which tumor necrosis factor (TNF) was added followed by glucose. TNF causes degradation and is associated with biomarkers of EC injury and hyperglycemia enhances vascular lesions [21]. In consequence, the plasmatic increase in the level of HA, marked with soluble or fluorescent biomarkers, correlates with the level of glucose in the blood, being two times higher in diabetics [22]. From these experi-

mental data, it follows that hyperglycemia can represent a therapeutic target to increase the chances of survival of the septic patient, and the MFD technology can be a useful platform to study the function of the endothelial barrier and the preclinical results of potential therapies.

GLYCOCALIX RESEARCH METHODS, RESULTS, AND LIMITATIONS

The GCX, being a fine structure, has been studied relatively recently, using confocal laser scanning, two-photon or atomic force microscopy methods. Using modern microscopy methods, it was possible to obtain imaging data on the barrier properties of the GCX and its interactions with blood components, both in static and in vitro perfusion models [23].

At present, in order to determine the degree of endothelial layer damage in sepsis, the GCX thickness is studied by calculating the distance between erythrocytes and endothelium [13]. Depending on the location, the pulsating voltage and the physical pressure exerted on the GCX, its thickness may vary. The observation technique and the type of vessel examined are also taken into account. The GCX is better visualized in the space between two continuous ECs, being thicker on the ECs of the arterioles, in the continuous and fenestrated capillaries [24].

Due to its electrical charge, the GCX exerts barrier properties and repels red blood cells (RBCs) that possess a degree of accessibility in the clear zone between them and the endothelium, forming the so-called perfused border region (PBR) [25]. Intravital microscopy coupled with immunofluorescence staining, associated with mathematical calculations, allows direct determination of GCX thickness and indirect determination by PBR calculation. RBC column width is typically 5-25 µm, with a mean PBR of 2.14 µm (range 1.43–2.86 µm). The low value of PBR indicates an efficient perfusion of the microvascular bed, while in sepsis it increases due to the penetration of RBC into the transparent zone [26]. Nonetheless, the PBR indicator cannot accurately determine the thickness of the GCX, as it depends on several factors. In the model of healthy control mice and those with sepsis, the reduction of GCX thickness was determined in the second group, which correlated with the degree of penetration of RBC, a marker of microvascular perfusion, into the transparent area, confirming the disorder [27].

The same conclusions were reached experimentally, following the reproduction of quantitative GCX measurements performed in real-time at the patient's bedside, in the emergency room and in the intensive care unit (ICU), of a university hospital. The physician and nurse in charge determined the sublingual microcirculation using the sidestream dark field (SDF) and the new data analysis software (GlycoCheck™) to determine the PBR [28]. Intravenous microscopic examination in combination with fluorescence is difficult to perform in clinical settings, therefore few studies have examined PBR parameters and RBC column width during sepsis. While SDF microscopy, the portable one, two-photon excitation microscopy (TPEF) or computerized technology, which made it possible to measure GCX thickness by computational means, are promising investigations in the early determination of sepsis [13].

Statistical data showed that measurement of circulating GCX components is an effective way to assess endothelial function and degree of GCX degradation. To develop an effective treatment in sepsis and septic shock, the GCX fragments present in the blood during sepsis are studied, which serve as clinical biomarkers, and their amount can be correlated with the severity of various diseases, including septic ones [24]. The added value of determining the GCX in clinical conditions is the early detection of endothelial dysfunction. Clinicians can intervene early by detecting signs of vascular damage by assessing the integrity of the GCX, which can also be used as a method to guide the individualized therapeutic approach. Patients with degraded GCX may benefit from targeted therapies aimed at restoring endothelial function, such as fluid management strategies or drugs that protect or restore the GCX (hydrocortisone, albumin or certain antioxidants). Also, values indicating damage to GCX integrity are a prognostic indicator and correlate with poor outcomes in critically ill patients. Monitoring of GCX degradation products in the blood, such as HA or SDC-1 [29], may help predict patient prognosis and severity of sepsis progression. In ICUs, evaluation of the GCX can guide fluid resuscitation strategies. By monitoring the GCX, clinicians can avoid fluid overloading patients and prevent further endothelial injury. The GCX plays a key role in microcirculatory regulation, and its assessment may serve as an additional marker of microcirculatory health, aiding in the evaluation and management of septic shock, in which microcirculatory insufficiency is a critical component [30].

Baseline SDC-1 levels can be used for early identification of high-risk sepsis patients, being a useful predictor of complications and mortality [31]. SDC-1 and SDC-3 levels were found to increase nearly 6-fold in sepsis patients, and the average concentration of HA, which in healthy people has values of 116 ng/mg, increases to values of 168 ng/mg in people with SIRS, and in sepsis it exceeds three times the reference values [32]. By direct measurement of HA in urine it can be calculated that approximately 1%, equivalent to 100-300 ng/ml, of the normal daily circulating volume is filtered by the kidneys, while in severe sepsis and septic shock, these

values are increased [33]. Based on the statistical data, we can conclude that the ratio of septic shock markers in patients who died in the first 3 months is significantly higher compared to severe trauma patients, neurosurgical patients or survivors of septic shock [34].

The loss of the GCX was demonstrated experimentally by using confocal and atomic force microscopy, studying in vitro the vascular response on the model of antagonism between growth factors of the angiopoietin group (Ang-1 and Ang-2) and their interaction with tyrosine kinase receptors (Tie1 and Tie2) [35]. Ang-2 overexpression induces vascular ECs migration and survival through Tie2 activation, suggesting a positive effect on angiogenesis. Ang-1/Tie2 signaling ensures support of vascular integrity, inhibition of inflammatory gene expression and prevention of leukocyte recruitment [36]. Ang-2 is secreted by ECs in pathological conditions, being an HPSE-dependent mediator. It competitively binds to Tie2 degrading HS, whose fragments stimulate the release of proinflammatory cytokines, thus increasing inflammation. SDC-4, at the place of attachment with the HS chain, becomes free when the GCX protective layer is damaged, favoring the adhesion of leukocytes and platelets. Hence, inhibition of Ang-2 and TIE2 activation leads to lower GCX clearance and increases the chances of survival in sepsis [37].

The consequence of GCX degradation is its inability to perform its normal functions, manifested by microcirculatory dysfunctions, which result in: increased vascular permeability and platelet aggregation; disordered vasodilation and increased adhesion of leukocytes; tissue edema and decreased plasma protein – the degraded layer of GCX becomes thinner, allowing transcellular and paracellular transport of water and macromolecules (plasma proteins) through the vascular wall [38].

Once the infection occurs, the GCX is activated under the action of inflammatory mediators, which normally exposes integrins and immunoglobulins (Ig), facilitating ligand-receptor interactions, which favor leukocyte adhesion [39]. However, it has been shown that the GCX tends to attenuate leukocyte adhesion and subsequent vascular damage by not displaying or inhibiting ECs adhesion molecules [40]. As the inflammation progresses, more and more leukocytes are tightly attached to the endothelium. As a result of such adhesion, within 2-4 hours of the onset of acute inflammation, the entire inner wall of the post-capillary vessels in the area of inflammation is covered with a layer of leukocytes. In response to systemic procoagulant stimuli, EC produces prostacyclin, tissue factor pathway inhibitor (TFPI) and HS [41], whose circulating fragments can bind to Antithrombin-III (AT-III) inhibiting factor Xa activity, but cannot inhibit thrombin [42]. Therefore, thrombomodulin binds to thrombin to form a complex that inactivates the clotting activity of thrombin. Or, at the site of HS attachment to SDC-4, circulating antithrombin (Hep cofactor-1) binds, increasing its inhibitory activity on thrombin and exerting an anti-inflammatory action. In consequence, antithrombin exerts beneficial effects on ECs function in sepsis, but its amount can be reduced by the increase of circulating endotoxin, participation in the formation of complexes with coagulation factors, proteolytic degradation by granulocytic elastase [43]. In conclusion, even though the endothelial surface lacking the GCX may be more prothrombotic, plasma HS elimination itself is antithrombotic [44].

ECs have the ability to inactivate pro-coagulant enzymes, which allows quantitative determination of the GCX by assays performed in vitro on native cultures of rat aorta and HUVEC. It has been shown experimentally that the weight of Hep in the aorta is 10-fold higher compared to HUVEC, which functionally means that HUVEC has 5 times less anticoagulant capacity (thrombin inactivation), compared to aortic tissue [45]. Blood flow is disturbed when the site of attachment of the Hep chain to SDC-4 becomes free following GCX degradation, with the subsequent development of microthrombi and reduced oxygen supply, which can result in organ failure. Although overall oxygen delivery is usually increased during sepsis, tissue capillaries do not receive adequate oxygen supply due to microvascular endothelial injury [46].

In general, the pathophysiological responses of the GCX work to isolate the infection, prevent the spread of microorganisms, and successfully eliminate them. However, in the case of a fulminant infection, the processes of leukocyte adhesion and thrombogenesis produce acute lesions in the host, contributing to the general morbidity and mortality in sepsis and septic shock [47]. It is currently known that GCX can react to inflammatory processes through chemokines, or through fibroblast growth factor (FGF). Chemokines are found near cell surfaces and the extracellular matrix. They have the role of controlling the direction of cell movement, which they exercise by attaching to the receptors of migrating cells. Also, through these receptors, chemokines interact with GAGs. During GCX degradation, the receptor becomes free, creating a gradient of transepithelial chemokines, which control the migration and attachment of neutrophils to damaged tissue, amplifying inflammation [48].

Another experiment, based on the spectrometry of human pulmonary microvasculature endothelial cells (HPMEC), aimed to determine the degree of damage to the repair mechanisms of the GCX during sepsis. When circulating HS simultaneously interacts with FGF and its receptor (FGFR), it acts as a stimulator of physiological GCX repair. But when it only binds the FGF ligand, it acts

as an inhibitor of its signaling. When the activated FGF protein binds to FGFR, a signal is released, which activates exotoxin-1 – the GCX repair molecule, with the role of an enzyme in the synthesis of HS. In sepsis, this repair process is significantly delayed because signaling from the activated FGFR receptor is inhibited [49]. In view of the above, we can see that the GCX is affected right from the beginning of sepsis, suggesting that stopping this process would have a strong therapeutic effect, which can probably be achieved by improving the GCX repair signal [50].

Laboratory and experimental techniques provide diagnostic information for sepsis based on GCX structures, but so far, no model has been created that provides all the data on GCX. Even the most innovative methods are limited in their ability to accurately quantify the presence of GCX or its metabolites. Currently, clinical tools to directly measure GCX thickness or degradation are not widely available. Most methods are experimental or limited to specialized research settings, making routine evaluation of the GCX challenging in everyday clinical practice. Measurement of GCX removal products such as SDC-1, HS or HA is based on indirect blood markers. These markers may not provide a complete or accurate representation of the actual state of the GCX in real-time or in different vascular beds. A universally accepted standard for GCX assessment in clinical settings has not yet been developed. Variability in measurement techniques, interpretation of results, and lack of consensus on cutoff values limit the utility of GCX measurements for routine patient management. The GCX is sensitive to various factors, including mechanical stress, changes in blood pressure, and inflammatory mediators. Systemic effects and endothelial dysfunctions present a wide spectrum, from which it is difficult to isolate GCX-specific lesions, being a challenge in a clinical setting. Even if measurement tools were available, the cost and time required for GCX assessment may preclude their routine use, particularly in resource-limited institutions. For large-scale clinical implementation, more accessible, faster diagnostic methods that ensure operational safety must be developed. Likewise, the method that would allow the determination of GCX in laboratory conditions in daily practice remains a research objective. Such a model would undoubtedly improve the study of sepsis and septic shock.

POTENTIAL THERAPEUTIC OPTIONS

Treatment management in sepsis is based on the list of 18 statements of high practical value "Guidelines for survival in sepsis" approved in 2016 by 25 international organizations, out of 93 proposed. One of these statements calls for fluid resuscitation with crystalloid or colloid solutions because sepsis causes tissue hypoperfusion [51]. The distribution of different types of crystalloids in the body depends on the integrity of the GCX. When this is disrupted, capillary permeability increases, which reduces the effectiveness of resuscitation fluids [52]. Volume supplementation with crystalloid and colloid solutions is becoming a vital necessity in patients with microcirculatory perfusion disorders and organ dysfunction, but requires prior evaluation of the benefits and harms resulting from the administration of these solutions [53]. Aggressive volume repletion leads to hypervolemia, to which the body responds by releasing atrial natriuretic peptide (ANP) from the heart and causing increased GCX excretion. In the presence of inflammation, serum ANP release increases significantly, accompanied by increased vascular permeability, 9- to 18-fold degradation of SDC-1 detectable by electron microscopy, rapid movement of intravascular fluid into the interstitial space, and cardiopulmonary complications [54].

Hydroxyethyl starch (HES), rather than other synthetic colloids, can restore GCX, which serves as a barrier to fluid and colloid exchange in the coronary vasculature. Maintenance of GCX thickness is possible due to the protective effect of HES130 6%, which reduces the plasma expression of SDC-1 [55]. Based on the two experiments, we conclude that in cases of shock, the administration of HES is preferable to crystalloids [13]. HES130 suppresses vascular permeability during fluid resuscitation, as demonstrated by direct visualization of GCX by intravital fluorescence-labeled lectin microscopy on mouse dorsal skinfold chambers (DSCs) with assessment of vascular permeability changes in vivo [56]. By intravital microscopy, using LPS models that increase vascular permeability, it was shown that the administration of 6% HES does not change GCX thickness, exerts protective effects and reduces the level of its degraded components in serum [57].

Albumin is a natural colloid derived from human plasma used worldwide to treat critically ill patients. Some studies have suggested that albumin can restore GCX. When large amounts of fluids are required to restore hemodynamic stability, albumin solutions can be a safe and effective alternative [58]. Albumin attaches to HA contained in the outer layer of GCX, playing an essential role in its stabilization and protection. In sepsis, the transendothelial transport of plasma proteins, especially albumin, is stimulated. Along with the depletion of plasma proteins, degradation of SDC-1, HS and CS also occurs [59]. GCX degradation can be mitigated by the administration of fresh frozen plasma and albumin which is commonly used to restore volume. In plasma, an important role belongs to the sphingolipid sphingosine 1-phosphate (S1P), which, being associated with albumin, participates in the regulation of GCX stability by modulating the activation of MMPs [60]. As a result of experimental research, it was shown that GCX does not suffer significant differences

in the group with albumin and HES130. Other studies have also concluded that although albumin allows faster withdrawal of vasopressor and inotrope therapy, its use is more expensive but may modestly reduce the mortality rate in patients with severe sepsis. Other differences between the administration of albumin or crystalloids in septic patients are not attested [61].

Although specific treatments aimed directly at GCX protection and restoration have not yet been developed for widespread clinical use, several strategies aimed at the potential to preserve or restore GCX integrity are addressed, primarily in the context of endothelial protection [62].

The effect of dexamethasone before LPS injection and doxycycline after LPS injection was investigated in experimental animal models. These preparations significantly inhibit the activity of MMPs, preserve the expression of SDC-1, and limit the inflammatory damage of the GCX. Doxycycline has a greater MMP inhibitory potency compared to dexamethasone, which possesses a greater ability to rescue SDC-1 expression [63].

Heparin can save the life of the septic patient and protect him/her from associated complications by exerting its anticoagulant and anti-inflammatory properties, by inhibiting HPSE, which removes HS from the GCX [64]. Heparin also functions as part of the innate immune system, as it participates in target sequestration by forming fibrin clots to which platelets attach. This complex is recognized by leukocytes, leading to the elimination of microorganisms by phagocytosis [65].

Based on experimental models of septic mice by exposure to LPS, the possibility of accelerating pharmacological recovery of the disintegrated GCX by administration of Sulodexide (SDX) was determined by atomic force microscopy in vitro. SDX – product purified extract from porcine intestinal mucosa, attenuates the clearance of HS and SDC-4 due to its properties of being similar to Hep and resistant to HPSE degradation, having the effect of accelerating the regeneration of the GCX in septic disorders [66]. At the same time, SDX was used as a method to treat diet-induced obese mice. In obese mice with hyaluronidase-induced stress, the extent of GCX degradation and the effect of SDX therapy on microcardiac perfusion were evaluated. Administration of Hyals, for the enzymatic degradation of GCX, completely reduced myocardial perfusion, but 4-week treatment with SDX partially restored myocardial perfusion in rats to +37% [67]. In conclusion, the adverse effect of acute GCX degradation and the long-term protective effect of SDX on myocardial perfusion provides indirect evidence for the role of GCX in maintaining coronary microvascular function [68].

Gentiopicroside (GENT) is the main active component of the traditional Chinese medicinal plant Radix Gentianae. In vitro it has been shown to act on macrophages by reducing the production of inflammatory cytokines, and in vivo it reduces the number of deaths among mice with septic shock, and decreases the serum levels and mRNA expression of IL-1β, IL-6 and TNFα [69]. Since inflammation is a primary driver of GCX degradation, particularly by activating enzymes such as HPSE and MMP, the anti-inflammatory effects of GENT could theoretically help protect GCX from damage during inflammatory responses, but more research is needed to establish a specific link between GENT and GCX.

Toddalolactone (TA-8) – the main compound isolated from Toddalia asiatica, inhibits the production of pro-inflammatory cytokines, decreases markers of LPS-induced liver damage, and attenuates inflammatory cell infiltration and tissue damage in lungs, liver and kidneys. Although TA-8 itself has not been widely studied, especially in relation to GCX, it remains an anti-inflammatory and immunosuppressive drug with a major impact in the treatment of sepsis and septic shock, which increases the chances of survival, and its properties suggest potential mechanisms that could benefit the endothelium, including through GCX protection [70].

DISCUSSION

GCX is a gelatinous structure that covers the inner part of the EC membrane, and which is made up of PGs, and sulfated and non-sulfated GAGs [10]. During sepsis, which is a hyperresponse of the immune system to infection, inflammatory mediators are released, capable of damaging GCX by cleaving the structures through MMPs, Hyals and HPSEs [9]. Thus, in serum GCX fragments SDC-1 and SDC-3 serve as early clinical biomarkers of sepsis, and in urine HA fragments, increased levels correlating with sepsis severity [32]. That is why, a special role belongs to the study of GCX repair mechanisms and how the degree of their degradation can be determined by HPMEC spectrometry [49]. Due to its electronegativity, the extent of damage to the endothelial layer can be determined both experimentally and clinically by calculating GCX thickness, these prognostic investigations being promising in early sepsis [13]. Knowing the major roles of GCX as a barrier, protection, and regulator of homeostasis, it is not surprising that the degradation of GCX is manifested by microcirculatory dysfunctions, and its participation in the processes of coagulation and adhesion of leukocytes on the EC surface has been thoroughly studied in vitro on native cultures of rat aorta and HUVEC [20]. Fluid resuscitation with crystalloid or colloid solutions is one of the most common methods of treatment in sepsis, but it remains a hot topic of discussion because

there is a risk of overloading the heart with volume and the subsequent development of complications [53]. HES is preferred over crystalloids because of the changes it produces on vascular permeability, which can be visualized in vivo by fluorescence-labeled lectin microscopy on mouse DSC [56]. The benefits of its use in the LPS model have also been demonstrated. In sepsis, the transendothelial transport of albumin is stimulated, and given its role in stabilizing and protecting GCX, its loss also results in a degradation of SDC-1, HS and CS [59]. Taking this into account, GCX degradation can be attenuated by the administration of plasma or albumin associated with the GCX stability-regulating sphingolipid S1P [60].

In this review, we have mentioned that: dexamethasone before and doxycycline after LPS injection limit the inflammatory damage of GCX [63], heparin can be lifesaving in sepsis due to its anticoagulant and anti-inflammatory properties [64], the pharmacological recovery of disintegrated GCX can be accelerated by administering SDX [66], which also has a protective effect on myocardial perfusion [68], the use of GENT or TA-8, due to its anti-inflammatory and immunosuppressive properties [69], could represent effective phytotherapeutic methods for treating sepsis and septic shock [70].

CONCLUSIONS

Given the major role of GCX as a central part of the pathophysiology of sepsis, it is clear that further studies are needed to determine the components that protect GCX from degradation and what the possibilities for repair are, in order to develop therapeutic strategies in sepsis. Delving into the complexity of GCX structure is an innovative modality that has immense potential in revolutionizing the diagnosis of sepsis, opening up new avenues of treatment and having real potential for use in preventive strategies against sepsis-induced organ failure.

ABBREVIATIONS

Ang – angiopoietin
ANP – atrial natriuretic peptide
AT-III – antitrombin-III
CA – chondroitin acid
CS – chondroitin sulfat
DSC – dorsal skinfold chambers
EC – endothelial cell
FGF – fibroblast growth factor
FGFR – fibroblast growth factor receptor
GAG – glycosaminoglycan
GCX – glycocalyx
GENT – Gentiopicroside
HA – hyaluronic acid
Hep – heparin
HES – hydroxyethyl starch
HPMEC – human pulmonary microvasculature endothelial cells
HPSE – heparanase
HS – heparan sulfat
HUVEC – human umbilical vein endothelial cells
Hyals – hyaluronidases
ICU – intensive care unit
Ig – immunoglobulin
LBP – lipopolysaccharide binding protein
LPS – lipopolysaccharide
MFD – microfluidic device
MMP – matrix metalloproteinase
PBR – perfused border region
PG – proteoglycan
RBC – red blood cell
S1P – sphingosine 1-phosphate
SDC – syndecan
SDF – sidestream dark field
SDX – Sulodexide
SOFA – sequential organ failure assessment score
TA-8 – Toddalolactone
TFPI – tissue factor pathway inhibitor
Tie – tyrosine kinase receptors
TNF – tumor necrosis factor
TPEF – two-photon excitation microscopy

AUTHORS' CONTRIBUTION

MA – Conceptualization, Formal analysis, Investigation, Writing (Original Draft), Visualization
AA – Conceptualization, Resources, Writing (Review & Editing), Visualization
CS – Visualization, Writing (Review & Editing)
MȘ – Validation, Supervision
CS – Validation, Writing (Review & Editing), Supervision

CONFLICT OF INTEREST

None to declare.

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