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SCIENTIFIC REVIEWS AND LECTURES

A.P. Vorobyeva, Y.V. Bykov, V.A. Baturin, A.A. Muravyeva, V.V. Massorov

# GLYCOCALYX DISORDERS IN CRITICAL CONDITIONS: PATHOPHYSIOLOGICAL AND CLINICAL ASPECTS

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**BYKOV Yuri Vitalievich** – PhD, assistant of professor of the Department of Department of Anesthesiology and Intensive care with a course of additional professorial education of Stavropol State Medical University, Federal State Educational Institution of the Ministry of Health of Russia, e-mail: yubykov@gmail.com, ORCID ID: https://orcid.org/0000-0003-4705-3823; **BATURIN Vladimir Alexandrovich** – MD, Professor, Head of the Department of Clinical Pharmacology, with the course of DPO of Stavropol State Medical University, Federal State Educational Institution of the Ministry of Health of Russia, e-mail:prof.baturin@gmail.com, ORCID ID: https://orcid.org/0000-0002-6892-3552; **VOROBYEVA Anna Pavlovna** – anesthesiologist-resuscitator of the intensive care and intensive care wards of G.K. Filippsky City Children's Clinical Hospital, Stavropol, e-mail: a.v.955@yandex.ru, ORCID ID:https://orcid.org/0000-0002-0082-1971; **MURAVYEVA Alla Anatolyevna** – PhD, assistant of professor of the Department of Department of Anesthesiology and Intensive care with a course of additional professorial education of Stavropol State Medical University, Federal State Educational Institution of the Ministry of Health of Russia, e-mail: muravyeva81@mail.ru, ORCID ID: https://orcid.org/0000-0002-4460-870X; **MASSOROV Vladislav Viktorovich** – resident of the department of Anesthesiology and Intensive care with a course of additional professorial education of Stavropol State Medical University, Federal State Educational Institution of the Ministry of Health of Russia, e-mail:Vladislav.massorov@yandex.ru, ORCID ID: https://orcid. org/0009-0008-4009-1783

**Aim:** to evaluate the results of clinical studies devoted to the study of the role of endothelial glycocalyx (GC) in the pathogenesis of critical conditions.

**Materials and Methods.** Scientific information was searched in domestic (E-Library) and foreign databases (PubMed, Scopus, Oxford University Press, Springer, Web of Science Core Collection). 120 publications were analysed, 42 of them were selected to meet the requirements of the review.

**Results.** GC is a gel-like polysaccharide-protein layer covering the surface of vascular endothelial cells. GC maintains homeostasis of the vascular network, including controlling vascular permeability and microvascular tone, preventing microvascular thrombosis, and regulating leukocyte adhesion. Endothelial GC damage is a universal link of pathogenesis in various pathological processes. The proposed review considers the structure and functions of GC, its participation in the pathogenesis of such diseases as diabetes mellitus, sepsis, covid-19, polytrauma, pre-eclampsia, epilepsy and others. A decrease in GC thickness in patients with diabetes mellitus has been described. The effect of hyperglycaemia on GC structure has also been noted. In sepsis, GC is damaged by free oxygen radicals, which are released by circulating leukocytes, which in turn triggers a cascade of reactions that lead to systemic oedema, hypovolaemia with further development of organ and tissue damage. In severe trauma, damage to GC is noted, which is accompanied by the release of syndecan, heparan sulfate, hyaluronic acid into the bloodstream. Preeclampsia is also associated with GC damage, which can be detected by elevation of specific markers. Epilepsy and many other neurological diseases are associated with disruption of the blood-brain barrier, whose dysfunction is associated with GC dysfunction.

**Conclusion.** Timely diagnosis of GC degradation can improve life prognosis and therapeutic outcomes in critically ill patients.

**Keywords:** glycocalyx, sepsis, pre-eclampsia, polytrauma, status epilepticus, coronavirus infection, syndecan, hyaluronic acid.

**Introduction**. At the present stage of medicine, the earliest possible diagnosis of glycocalyx (GC) dysfunction in critical conditions is extremely important, since its structure disorder is a predictor in the development of many pathological processes and their complications [1]. This issue is especially acute in the practice of intensive care physicians, since timely diagnosis of GC disorders can improve the prognosis of the course of the disease and increase the chances of survival [2]. GC damage and development of endothelial dysfunction are a component in the pathogenesis of many diseases, such as diabetes mellitus (DM), cardiovascular diseases, strokes, epilepsy, which are widespread in the clinic of critical conditions [31]. Modern methods of GC dysfunction assessment, which are the most

applicable for use in practice, include dark-field microscopy of the superficial microcirculatory bed and enzyme immunoassay, which is used to detect the main components of endothelial GC, such as syndecan, glypican, heparan sulfate, hyaluronic acid, etc. [1]. It has been shown that earlier determination of GC destruction markers in the blood is able to predict the development of severe complications and allows to judge about the unfavourable course of the disease, which can be useful in the practice of intensive care physician in order to carry out the correction of modern methods of treatment [31] .

The aim of this review was to analyse modern literature sources describing GC damage in various critical condition.

Structure and functions of the glycocalyx GC is a general term for polysaccharide protein complexes that coat the surface of vascular endothelial cells (ECs) [1]. GC is a complex, negatively charged gel-like layer on the lumenal side of ECs, composed of glycosaminoglycans (GAGs), which are bound to membrane spanning proteins and glycoproteins characterised by short branched carbohydrate side chains [2]. The GAGs that make up GC are primarily heparan sulfate, chondroitin sulfate and hyaluronic acid (also called hyaluronan or hyaluronan) [2].

Notably, the dynamic balance between biosynthesis and excretion makes it rather difficult to correctly describe the geometric location and distribution of GC [11]. GC has a total negative charge that helps to determine interactions with proteins [22]. In particular, it can adsorb positively charged regions of some plasma proteins and complements the barrier function of the endothelium by acting as a first barrier to leakage of plasma proteins (which are mostly negatively charged, such as albumin) into the interstitium [2]. In addition, by preventing protein leakage from the vascular network, GC helps to maintain osmotic pressure towards the blood vessel lumen, thereby preventing water from entering the tissues [22]. Finally, GC has antithrombotic/profibrinolytic effects and also inhibits neutrophil/leukocyte attachment [22]. Several components of GC including syndecans, heparan sulfate and hyaluronic acid are altered in cases of ischaemia, hypoxia, sepsis, atherosclerosis, renal disease, DM and some viral infections [19]. This alteration has a negative impact on the endothelium, leading to microcirculatory dysfunction with subsequent organ ischaemia and subsequent organ damage [22].

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**Diagnosis of glycocalyx disorders in some critical conditions.**

**Sepsis**. Sepsis is defined as life-threatening organ dysfunction caused by dysregulation of the host organism's response to infection [38]. Sepsis and septic shock are accompanied by severe endothelial damage and degradation of GC, leading to dysregulation of homeostasis and vascular wall permeability, causing damage to the microcirculatory channel [40]. GC plays a key role in the physiology of the microcirculatory system and endothelium and is involved in the regulation of microcirculatory channel tone and vascular permeability, maintenance of oncotic gradient across the endothelial barrier, as well as leukocyte adhesion/migration and prevention of thrombosis [3]. Conformational changes in GC structure lead to the release of nitric oxide, which contributes to the regulation of vasomotor tone and tissue perfusion [14]. Local and systemic inflammation leads to changes in the structure and physiology of GC and, as a result, to endothelial dysfunction [4]. GC degradation during inflammation is associated with increased capillary permeability and release of albumin and fluid into the intercellular space [4]. Degradation of heparan sulfate leads to a procoagulant state with subsequent microthrombosis and loss of antioxidant properties with progressive oxidative damage to the endothelium [4].

Insufficiency of the endothelial system and GC against the background of sepsis triggers the mechanism of multi-organ failure (MOF). The main triggers of MOF are proinflammatory mediators, including interleukin-1 (IL-1), IL-2, IL-6, tumour necrosis factor (TNF) and other molecules released during inflammation (bradykinin, thrombin, histamine, vascular endothelial growth factor), which cause damage and activation of GC components during septic shock, as well as stimulate the release of intercellular and vascular cell adhesion molecules [23]. These mediators lead to accumulation, adhesion and migration of leukocytes, which triggers inflammatory processes in endothelium and tissues and leads to further GC damage with progression of capillary leakage into the interstitial space [23].

Some clinical studies have reported that on the day of admission to the intensive care unit (ICU), patients with sepsis had significantly higher median plasma concentrations of GC and heparan sulfate compared to controls, with those who died within the next 90 days having significantly higher GC concentrations in the sepsis patient population [29].

More recently, the plasma concentration of syndecan-1 (SDN-1) in patients with septic shock was found to be more than twice as high as in healthy volunteers on day 1 of admission to the ORIT and was significantly associated with the SOFA total score (a scale to assess the likelihood of sepsis in patients in the ORIT) and the SOFA coagulation subscale [33]. In cases of sepsis, the blood coagulation system may become pathologically activated, leading to disseminated intravascular coagulation syndrome and thrombosis. Measurement of whole blood coagulation in patients with sepsis may reveal hypo-, normal or hypercoagulable state, while conventional laboratory tests may show that plasma is not hypercoagulable per se, leading to the hypothesis that endothelial dysfunction may be a major contributor to DIC syndrome [30].

According to another paper, hyaluronic acid and SDH-1 concentrations were higher during the first five days in the ORIT of patients with severe sepsis (sepsis with acute organ dysfunction) and septic shock (sepsis with refractory hypotension despite adequate fluid load) compared to patients with sepsis [6]. In addition, levels of GC and SDH-1 were elevated for at least the first 3 days in patients with septic shock compared to

patients with severe sepsis. More importantly, in surviving patients, GC and SDH-1 concentrations tended to decrease during the ORIT stay, whereas in non-surviving patients they tended to be slightly elevated or remained unchanged [6]. Thus, monitoring the progression of markers of GC damage (e.g. hyaluronic acid or SDN-1) may be useful for assessing sepsis progression and predicting survival.

**Severe trauma/polytrauma**. Despite modern advances in the prevention and treatment of severe trauma, traumatic injuries continue to be the leading cause of morbidity and mortality in children and adults worldwide [16]. It has been found that after initial direct injury to the vascular surface and subsequent inflammatory response, persistent disruption of GC integrity leads to the development of vascular dysfunction in adults with traumatic injuries, culminating in organ dysfunction [27]. Trauma-induced coagulopathy may begin with a state of hypercoagulability that progresses to hypocoagulability, or vice versa, and may depend on several factors, including the degree of injury, the amount and rate of intravascular fluid administered, and the presence of excessive fibrinolysis [26]. Blood concentration of SDN-1 was elevated in trauma patients after admission to the ORIT, and patients with higher than average SDN-1 concentration showed more signs of microcirculatory dysfunction [28].

While microcirculatory dysfunction improved over time and SDN-1 concentration decreased, SDN-1 remained elevated for 30-50 h compared to healthy controls [27]. According to a study [21], intensive care for adults with traumatic haemorrhagic shock usually includes balanced transfusion of blood product components (administration of equal volumes of fresh frozen plasma and platelets with transfused red blood cells). On the other hand, haemorrhagic shock after severe trauma does not usually occur in children, which is probably due to the epidemiology of the injury and the nature of the injury (i.e. more isolated head trauma). In addition, those children who present with trauma-related haemorrhagic shock that does not require massive transfusion are more likely to be resuscitated with crystalloid fluid and packed red blood cells without a balanced transfusion approach [34]. However, this strategy may lead to worse clinical outcomes and has been questioned [34]. Although trauma itself leads to GC degradation, the choice of intravenous resuscitation solution also contributes. When healthy subjects were administered 0.9% saline, Hartmann's solution, 4% and 20% albumin in a double-blind crossover study, only 0.9% saline showed GC degradation due to an increase in plasma SDH-1 content [7]. In resuscitation of patients with haemorrhagic trauma, an approach with limited use of saline solution is recommended and emphasis is placed on balanced transfusions including fresh frozen plasma [31].

**Pre-eclampsia**. Pre-eclampsia (PE) is one of the most serious complications of pregnancy, ranking third in the list of causes of maternal mortality and is a major cause of neonatal morbidity and mortality [9]. Currently, pulmonary embolism is considered as a multisystem pathological condition with clinical manifestations beginning after the 20th week of pregnancy [9]. It is characterised by arterial hypertension combined with proteinuria and often oedema and signs of multi-organ/polysystemic failure[9].

The pathophysiology of PE is not fully elucidated, but most agree that varying degrees of impaired placental perfusion result in the release of soluble factors into the maternal bloodstream, leading to maternal endothelial dysfunction [39]. The development of placental ischaemia is characterised by increased apoptosis in placental structures and the entry of necrotic debris and microparticles of trophoblastic origin into maternal blood [32]. These changes initiate the triggering of a systemic inflammatory response: activation of immune cells and complement system, synthesis of proinflammatory cytokines and, consequently, the development of endothelial dysfunction [32]. GC release causes capillary leakage leading to oedema and proteinuria, dysregulation of vascular tone leading to hypertension and impaired microcirculation, activation of the blood coagulation system causing platelet consumption, and inflammatory changes [20].

Maternal plasma concentrations of SDH-1 increase during pregnancy and reach concentrations comparable to those in sepsis at term [24]. Circulating concentrations of hylauronic acid are elevated in PE compared to normotensive pregnancies [41].

Circulating concentrations of GC degradation products are elevated in PE compared to normotensive pregnancies. Thrombomodulin as a marker of endothelial damage in PE has been associated with disease severity and may be useful in at-risk women with PE [8]. Evidence that endothelial GC is an important pathophysiological link in PE requires further investigation [8].

**Status epilepticus**. Status epilepticus (SE) is a frequent life-threatening emergency in which patients suffer from continuous or rapidly recurring seizures [5]. These incessant seizures lead to death, accelerate the progression of epilepsy and reduce the quality of life [5]. Normal neuronal function and brain homeostasis require blood-brain barrier (BBB) interaction [42]. The HEB is a dynamic and complex neurovascular unit that protects the brain parenchyma from circulatory factors and regulates and maintains the stability of the internal environment of the central nervous system [42]. Recently, the GC has been identified as a component of the extended neurovascular system, an important physiological structure that maintains proper neuronal homeostasis [10]. GEC disruption has been described in several neurological diseases [18]. Recently, it has been reported that seizure frequency in epilepsy increases with an increase in the permeability of the GEB [18]. Cerebral herniation syndrome, intracranial hypertension, and cerebral oedema during epilepsy have been shown to be key causes of early death [17]. A vicious circle is formed between cerebral oedema and prolonged seizures, exacerbating cerebral oedema, accelerating the progression of epilepsy and worsening the outcome of patients with epilepsy [17].

Lee et al. described a decrease in GC levels compared to controls, following status epilepticus (SE), which was ameliorated by heparin. GC impairment was associated with higher GEC permeability and increased brain oedema 72 h after ES, as well as decreased survival and worse neurological outcome. Conversely, preservation of GC by heparin could reduce ES-induced glia cell activation, GEC leakage, brain oedema, reduce the expression of inflammatory factors and improve neurological outcome. The study highlights the importance of GC degradation in brain oedema and ES outcome, and indicates that heparin treatment may be a novel strategy for brain protection in ES [25].

**Coronavirus infection (Covid-19).** Although coronavirus 2019 (COVID-19) is a recently emerged SARS-CoV-2-related disease, numerous studies have rapidly identified microvascular injury and GC degradation as the main pathophysiological mechanisms of the disease [36]. Similar to bacterial sepsis, GC damage in COVID-19 follows a familiar pattern, and the GC degradation and endothelial damage observed in COVID-19 results in a prothrombotic state that leads to multi-organ thrombosis in severe cases [36].

Fraser et al. obtained data indicating that GC degradation was greater in patients with COVID-19, in contrast to age- and sex-matched ORIT patients without COVID-19, possibly explaining the greater risk of thrombosis in COVID-19. Compared with COVID-19-negative sepsis patients, COVID-19-positive patients had consistently higher levels of soluble P-selectin, hyaluronic acid, and SDN-1, especially on day 3 of the ICU and thereafter. In fact, SDN-1 levels continued to increase during the 7 days that COVID-19 patients were tested [13].

Fraser DD et al. published a case report of a 15-year-old female admitted to the hospital with COVID-19-related multisystem inflammatory syndrome (MIS-C) and demonstrated that plasma GC levels were elevated almost 7-fold compared to age- and sex-matched controls [13]. Measurement of the perfused border region of the hyoid blood vessels has become a useful bedside indicator of GC damage. It has been shown that ventilated COVID-19 patients have thinner GCs compared to non-ventilated COVID-19 patients or healthy controls [Rovas A, 2021]. The same study showed that plasma GC concentrations were significantly higher in both ventilated and non-ventilated patients with COVID-19 compared to controls, while SDN-1 was higher in ventilated patients with COVID-19 compared to both non-ventilated and control groups [37]. Studies using cultured endothelial cells treated with COVID-19 patient plasma in vitro have found similar changes in GC as well as hyaluronidase and cathepsin activity [35]. Several studies show that markers of GC degradation in blood correlate with disease severity in COVID-19 patients. The serum concentration of SDN-1 during the first day of admission to the ORIT was significantly higher in non-surviving COVID-19 patients compared to survivors [43].

Taken together, the published studies strongly suggest that GC clearly undergoes significant degradation as a result of COVID-19, which likely contributes to platelet adhesion and the increased risk of thrombosis seen in many COVID-19 cases. Thus, therapies aimed at inhibiting platelet adhesion (e.g. administration of nitric oxide via inhalation or by donor) and protecting/restoring GC (e.g. sulodexide and/or sphingosine-1-phosphate) may be indicated therapeutically [31].

**Conclusion**. The examples of the described nosologies demonstrate the undoubted clinical value of GC assessment, which serves as an impetus for further research in this field. Methods for assessing GC degradation, given its involvement in the development and progression of many disease groups, are of great importance in the work of clinicians. The possibility of drug correction of GC disorders is of great scientific interest. Despite the abundance of basic and preclinical studies of strategies to preserve and restore GC, human clinical trials are still lacking. In the paediatric population, there are still few studies on GC, which should also prompt future research.

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