

Vascular Endothelial Damage: The Role of Syndecan-1 and Hyaluronan as Severity Indicators in COVID-19

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ABSTRACT

SARS-CoV-2 was firstly found in bronchoalveolar lavage (BAL) of three suspected COVID-19 patients at Jinyintan Hospital, Wuhan, Hubei Province, China. The cases are still raising with 2,12% global mortality rate. Hypoxic respiratory failure due to acute respiratory distress syndrome (ARDS) is the main cause of COVID-19 death. Endothelial cell damage has an important role in the pathogenesis of ARDS and multi-organ dysfunction of COVID-19 patients. The endothelium is protected by mural cells, which keep vascular integrity. Inflammation is prevented by these cells by inhibiting the interaction of immune cells and platelets with endothelial cells. These cells also prevent coagulation by producing glycocalyx, coagulation inhibitors, and blood-clotting enzyme. Vascular glycocalyx has an important role to maintain endothelial function and is disrupted systemically in elderly and patients with various comorbidities, which can be a probable mechanism for the serious complications of COVID-19. Glycocalyx disruption in severe and critical COVID-19 patients causes increased levels of its components such as syndecan-1 and hyaluronan in the serum. Previous studies showed the significant increase of syndecan-1 and hyaluronan levels in septic, and severe Kawasaki and dengue patients. These biomarkers are also markers of organ damage. Therefore, hyaluronan and syndecan-1 can be significant prognostic factors for morbidity and survival in patients with COVID-19.

Keywords: glycocalyx; Covid-19; hyaluronan; syndecan-1

INTRODUCTION

SARS-CoV-2 was firstly found in bronchoalveolar lavage (BAL) of three suspected COVID-19 patients at Jinyintan Hospital, Wuhan, Hubei Province, China (Zhu et al., 2020). This virus is an unsegmented positive stranded RNA virus and has four main structural proteins (Lu, n.d.). SARS-CoV-2 is round/oval which can be inactivated by UV light or high temperature 56°C for 30 minutes (Olsen et al., 2003).

As of early August 2021, according to WHO data, it is known that the number of confirmed cases of COVID-19 is 199,466,523 and the number of deaths is 4,244,541. The case fatality rate is 2.12%. The first COVID-19 cases were reported on March 2, 2020 in Indonesia with a total of two cases. Data as of early August 2021, there were 3,532,567 cases of COVID-19 with 100,636 death cases and a mortality rate of 2.85% (WHO, 2021).

Currently, patients with COVID-19 are the main source of infection (Hoehl et al., 2020). Transmission in COVID-19 cases is through droplets (Han et al., 2020). Several cases have also reported that this virus is capable of transmitting to pregnant women and fetuses, although with a small vertical transmission rate (Chen et al., 2020). The incubation period for SARS-CoV-2 averages 1 to 14 days, most requiring 3-7 days (Chen et al., 2020). However, another study showed that incubation can occur for up to 24 days (Guan et al., 2020).

DISCUSSION

Inflammation, Immunity, and COVID-19

The pathogenesis of SARS-CoV-2 is still not widely known. On the other hand, the S protein in the corona virus is known to play an important role in the process of virus invasion into host cells where it will bind to the receptor Angiotensin converting enzyme 2 (ACE2) (De Wit et al., 2016). Viral and host factors play a role in SARS-CoV infection. The cytopathic effect on the virus and the ability to fight the immune system determines the severity of the infection. Dysregulation of the immune system further contributes to tissue damage caused by SARS-CoV-2 infection. Inadequate immune response leads to viral replication and tissue damage. On the other hand, excessive immune response can also cause tissue damage.

The immune response caused by SARS-CoV-2 is also not known with certainty. However, it can be studied based on the mechanism that occurs in SARS-CoV and MERS-CoV infections. When the virus enters the cell, the viral antigen will be presented to the antigen presentation cell (APC). The results of a study of patients who had recovered from SARS showed that after 4 years, CD4+ and CD8+ memory T cells were specific for SARS-CoV, but their numbers decreased gradually in the absence of antigen (Prompetchara et al., 2020).

It is known that viral mechanisms are created to evade the host's immune response. SARS-CoV can produce double-membrane vesicles that lack pattern recognition receptors (PRRs) and replicate within these vesicles so that they cannot be recognized by their host. The IFN-I pathway is also inhibited by SARS-CoV and MERS-CoV. Antigen presentation can also be inhibited in infections caused by the presence of MERS-CoV (Guan et al., 2020).

COVID-19 and Vascular Endothelial Dysfunction

The main cause of death in COVID-19 patients is hypoxic respiratory failure due to acute respiratory distress syndrome (ARDS) (Wu & McGoogan, 2020). The recent studies have shown that these cells contribute to the initiation and propagation of ARDS by impairing the integrity of the vascular barrier, triggering pro-coagulation conditions, inducing vascular inflammation (endolithitis), and mediates inflammatory cell infiltration (Varga et al., 2020). Therefore, a better understanding of the role of vascular disorders is very important (Teuwen et al., 2020).

The endothelium, under conditions of homeostasis, is surrounded by mural cells (pericytes), which maintain vascular integrity and barrier function. These cells prevent the interaction of endothelial cells with immune cells and platelets and inhibiting clotting glycoalyx (a protective layer composed of glycoproteins and glycolipids) with anticoagulation activity (Varga et al., 2020).

Then 30% of hospitalized patients with COVID-19 develop clinical deterioration with progressive lung damage, as a result of an exaggerated inflammatory response. Pulmonary complications, mechanically, result from breakdown of the vascular barrier, resulting in tissue edema (leading to accumulation of fluid in the lungs), endothelium, activation of the coagulation pathway with potential for disseminated intravascular coagulation (DIC) and unregulated inflammatory cell infiltration. As in ARDS due to other causes, endothelial cell damage has a central role in the pathogenesis of ARDS and multi-organ failure in COVID-19 (Wu & McGoogan, 2020).

Cardiovascular disease is also associated with increased mortality in hospitalized COVID-19 patients (Mehra et al., 2020). According to a previous report in Wuhan, 48% of patients had comorbid diseases, including hypertension (39%), diabetes (19%), and coronary heart disease (8%). Furthermore, patients with coronary risk factors and cardiovascular disease had the highest mortality rate (10.5%) from SARS-CoV-2 infection (Driggin et al., 2020). Data have shown that COVID-19 patients aged over 60 years have more systemic symptoms and pneumonia with more severe degrees than patients aged less than 60 years (Chan et al., 2020).

Multivariable regression analysis showed an increase in in-hospital mortality in elderly patients. This suggests that COVID-19 tends to worsen more easily in elderly patients with comorbidities, leading to immune dysfunction in elderly COVID-19 patients.

In other words, microvascular leakage, which acts as a window for SARS-CoV-2 invasion of organs, is caused by more severe damage to the endothelial glycoalyx in the elderly (Yamaoka-Tojo, 2020).

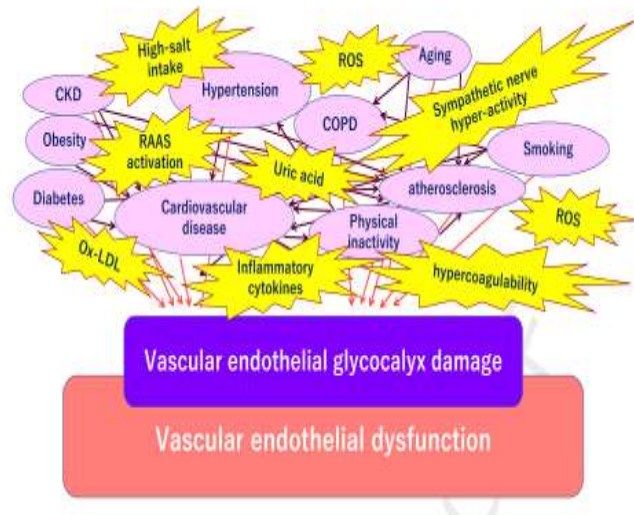


FIGURE 1: Comorbidities associated with worsening of COVID-19 and damage to the vascular endothelial glycoalyx.

Damage to the vascular endothelial glycoalyx is caused by various factors such as smoking, physical inactivity, hypertension, diabetes, obesity, and cardiovascular disease. SARS-CoV-2 can easily infect the microvascular endothelial glycoalyx that has been compromised, which is more common in the elderly than in the young, and more in men than women. ARDS: Acute respiratory distress syndrome, DIC: Disseminated intravascular coagulation, CKD: Chronic kidney disease, ROS: Reactive oxygen species, RAAS: Renin-angiotensin aldosterone system, COPD: Chronic obstructive pulmonary disease.

Vascular Endothelial Glycoalyx

The vascular endothelium is covered by a protective layer on its luminal surface called the glycoalyx. Glycoalyx is a gel-like layer composed of glycoproteins containing sialic acid, membrane proteoglycans (syndecan and glypican), side chain glycosaminoglycans (such as heparin sulfate and chondroitin sulfate), and long chain hyaluronan (HA). Glycoalyx functions to maintain endothelial permeability, regulate leukocyte migration, and inhibit intravascular coagulation (Lipowsky, 2019). Hyaluronan (a glycosaminoglycan) and syndecan (a proteoglycan) play an important role in maintaining the integrity of the glycoalyx. Vascular endothelial glycoalyx is stabilized by shear stress, which has a central role in its production (Curry, 2005).

On the other hand, homeostasis is impaired and degraded vascular endothelial glycoalyx under the presence of endotoxin in excessive levels, hyperglycemia (Pahwa et al., 2016), consumption excessive salt (Rorije et al., 2019), hypertension, familial hypercholesterolemia, and oxidized low-density lipoprotein (ox-LDL). In addition, unhealthy lifestyles such as smoking and physical inactivity also trigger glycoalyx degradation (Ushiyama et al., 2016).

Syndecan-1 and Hyaluronan as Biomarkers of Vascular and Organ Endothelial Glycocalyx Damage

Glycocalyx fragments, such as syndecan-1 and/or hyaluronan, have been studied, and their validity is currently being tested. Glycocalyx damage, characterized by increased concentrations of glycocalyx fragments such as plasma syndecan-1 and hyaluronan, has attracted the attention of critical illness experts. It is thought that this glycocalyx fragment is a diagnostic and prognostic indicator in various pathological conditions. The glycocalyx also functions as a barrier for albumin filtration. Therefore, glycocalyx fragments can be a biomarker in kidney disease. Although estimates of the role of this glycocalyx component have been made in several previous studies, it remains important to measure its prognostic value in future studies so that it can be used in the management of critically ill septic patients. This information can help complement routine biomarkers such as procalcitonin (PCT) and C-reactive protein (CRP) (Dane et al., 2015).

In the cohort study by Anand et al, hyaluronan and syndecan levels were significantly increased in septic patients compared to healthy individuals. The levels of both are even higher in severe sepsis and septic shock than in other septic patients. Hyaluronan and syndecan were also significantly different in survivors and non-survivors ($p < 0.001$). In this study it was stated that the cut off values for predicting mortality were 441 ng/ml and 898 ng/ml for hyaluronan and syndecan, respectively. Both markers were significantly correlated with APACHE II scores and SOFA scores (Anand et al., 2016). Systemic damage to the smooth lining of the vascular glycocalyx causes increased amounts of protein and water to move into the extra-vascular space which causes an increase in vascular permeability and causes interstitial edema in various organs (Uchimido et al., 2019).

Research on vasculopathy in viral infections, it is known that much has been suggested about the relationship between dengue fever and damage to the vascular endothelial glycocalyx, has been developing. It is known that dengue virus nonstructural protein 1 (NS1) is the only complex marker membrane protein that is replicated across cellular membranes. This evidence is the scope that it is important to revise and evaluate glycocalyx therapy, including in the context of COVID-19 (Yamaoka-Tojo, 2020).

On the other hand, patients with disease tend to develop systemic endothelial glycocalyx disruption due to complex mechanisms. Because through the process it is known that when the patient is infected with SARS-CoV-2, endotheliopathy due to systemic vascular inflammation through COVID-19 is very likely to develop into serious complications. As is the case in Kawasaki Syndrome where it is known that the production of inflammatory cytokines is said to be excessive and has a tendency to be unresponsive to IVIG. In fact, experts also point out that there has been a slight increase in the number of children with COVID-19 symptoms severe, where the condition is

similar to the characteristics of Kawasaki Disease Shock Syndrome (Ohnishi et al., 2019).

It is known that the ACE2 receptor, which also acts as a SARS-CoV-2 receptor, is also present on vascular endothelial cells and arterial smooth muscle cells in all organs. Recent studies on COVID-19 patients have shown that SARS-CoV-2 is capable of producing endothelium in various human organs (Varga et al., 2020). In fact, this is reported to be consistent with the incidence of systemic inflammatory disease similar to Kawasaki disease in COVID-19 patients. It is known that this condition is characterized by inflammation, one of which occurs in the walls of blood vessels, which increasingly shows that Covid-19 is a disease that is associated with thrombosis and endothelial dysfunction (Okada et al., 2021).

In experimental studies, it was explained that together with other pathophysiological conditions, disruption of the vascular endothelium in vital organs often causes organ damage (Boisrame-Helms et al., 2013). Therefore, elevated levels of syndecan-1 and hyaluronan may be associated with specific organ damage. In the research of Neves et al. (2015), revealed that plasma levels of syndecan-1 can be a predictor of the risk of acute kidney failure, hospital death, and mortality within 6 months (de Oliveira Neves et al., 2015).

Besides being the main component of the endothelial glycocalyx (Chappell et al., 2009), HA (Hyaluronic Acid) is also an important component of the extracellular matrix of the lung. In the research of Hallgren et al. (1989), the investigators correlated serum HA concentrations and BALF with lung injury score [Lung Injury Score (LIS)] and systemic severity as measured by SOFA score. The authors reported a positive correlation between serum HA levels and BALF at day 0 and LIS values, particularly through the association between HA levels and the degree of hypoxemia and PEEP. By looking for the relationship between HA levels and SOFA scores as an index of systemic severity, Esposito et al. (illustrating that, on the one hand HA levels in BALF only positively correlated with the respiratory component of SOFA scores, serum HA levels were elevated in patients with worsening respiratory, coagulation, hepatic, cardiovascular and renal failure, based on evaluation of SOFA scores.

CONCLUSION

Through the reading process, it can be indicated that serial measurements of hyaluronan and syndecan are important. These biomarkers are significant prognostic markers for morbidity and survival in patient of Covid-19. Then, based on the description, vascular endothelial damage has an important role in the pathogenesis of severe and critical COVID-19.

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