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ENDOTHELIAL DYSFUNCTION AND PULMONARY LESIONS IN LONG-COVID

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This review analyzed current scientific research data regarding the role of endothelial dysfunction in the pathogenesis of Long-COVID, specifically examining its impact on the alveolar-capillary membrane and the development of pulmonary complications. The potential of endothelial dysfunction biomarkers for diagnosis, prognosis, and the development of new therapeutic strategies was evaluated.

Analysis of open scientific data revealed that SARS-CoV-2-induced endothelial dysfunction was a key factor in the development of Long-COVID, leading to alterations in the alveolar-capillary membrane. Consequently, the development of interstitial lung diseases with fibrosis, impaired diffusion, and microcirculation was initiated, resulting in decreased tissue oxygenation. The pivotal role of endothelial function and alveolar epithelial status disorders, reflected in changes in Angiopoietin-1 (Ang-1), Angiopoietin-2 (Ang-2), von Willebrand factor (vWF), P-selectin, Intercellular adhesion molecule 1 (ICAM-1), Vascular endothelial growth factor (VEGF), and Krebs von den Lungen-6 (KL-6) levels, in the development and severity of pulmonary complications in patients with post-COVID syndrome was established.

This study expands the scientific and practical knowledge of medical professionals regarding the role of endothelial dysfunction biomarkers in the development of pulmonary complications associated with Long-COVID, and demonstrates their potential for diagnosis, prognosis, and the development of new therapeutic strategies.

Key words: *Long-COVID; COVID-19; endothelial dysfunction; biological markers; respiratory system; strong health.*

In December 2019, a new single-stranded RNA virus called severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) emerged that causes COVID-19 and has a wide range of clinical manifestations [1]. The COVID-19 pandemic has become a global health crisis that has led to a significant increase in mortality. According to the WHO, in May 2023, the total number of deaths exceeded 6.86 million [2]. As the acute phase of the COVID-19 pandemic is over, researchers are increasingly focusing on the long-term effects of the disease on recovering patients.

One of the main challenges is the growing prevalence of the long-term post-COVID syndrome known as Long-COVID. Epidemiological studies indicate that 65 million people worldwide suffer from Long-COVID, about 10 % of the total population who have contracted COVID-19 and 50-70 % of patients with severe disease [3, 4]. Long-COVID is a disease associated with prolonged symptoms caused by COVID-19 that last more than 12 weeks after acute SARS-CoV-2 infection and cannot be attributed to other possible causes [1, 5, 6]. Patients can be classified into three groups according to the development of Long-COVID. The first group is characterized by persistent symptoms caused by the direct cytopathic effect of the virus. The second group includes people whose symptoms are associated with the effects of prolonged hospitalization and/or intensive care. The third group is represented by cases where symptoms develop after complete clinical remission [3, 7, 8]. To date, more than 200 symptoms of Long-COVID are known, the most common of which are fatigue, muscle weakness, sleep disturbances, shortness of breath, cough, anxiety, and depression [9]. Various organs can be affected, but the lungs are the most vulnerable in patients with COVID-19, both during the acute illness and recovery stages [10-13].

Respiratory system damage in Long-COVID can vary in severity, with the most severe and clinically significant being interstitial lung damage followed by the development of pulmonary fibrosis [14]. Functional changes accompanied by a decrease in lung capacity of up to 80 % were observed in 39 % of patients with severe COVID-19 [15]. In addition, patients with moderate COVID-19 have significant respiratory limitations a year after recovery, which is manifested by a persistent decrease in lung diffusion capacity (DLCO) and the development of fibrosis. In one-third of cases, these impairments are significant, indicating a significant impact of the disease on pulmonary function [16-18].

Endothelial dysfunction is currently considered to be one of the most important mechanisms of Long-COVID pathogenesis and, in particular, lung damage in this pathological condition [19-22].

The endothelium of blood vessels consists of a single layer of endothelial cells that form the intima, which lies on the inner layer of blood vessels and is protected by pericytes [23]. The inner surface of the vascular endothelium is covered with glycocalyx, which regulates inflammation and vascular permeability [24]. Endothelial cells release vasoconstrictor factors, such as endothelin-1 (ET-1), prostaglandins, and angiotensin II. On the other hand, they are able to synthesize vasodilators, such as nitric oxide, prostacyclin, and natriuretic peptide [25]. Under normal circumstances, the endothelium also has an anticoagulant phenotype, which is reflected in the constant expression of plasminogen activator inhibitor-1 (PAI-1), von Willebrand factor (vWF), P-selectin, and tissue factor (TF) [1].

Pulmonary endothelial cells are the main barriers between the blood and the interstitium. They make up one third of the cells in the lungs. The alveolar-capillary membrane (0.1 μm thick) is responsible for gas exchange and consists of alveolar epithelium (types I, II) and endothelium [26]. It is the type II alveolar epithelium that is the main target cell for SARS-CoV-2 [12].

Endothelial dysfunction can be the result of both direct exposure to SARS-CoV-2 and an inflammatory immune response [18,27,28]. It has been shown that SARS-CoV-2 is able to infect endothelial cells (EC) via the angiotensin-converting enzyme 2 (ACE2) receptor and transmembrane serine protease 2 (TMPRSS2) protein. According to recent studies, SARS-CoV-2 can spread inside human microvascular endothelial cells (HMVECs) and, as a result, they are activated with subsequent dysfunction [20, 33]. The inflammatory process due to the immune response induced by SARS-CoV-2 is characterized by hyperactivation of the immune system, which is manifested by the development of a cytokine storm with hypersecretion of proinflammatory cytokines (in particular, IL-1, IL-6 and TNF-α), leading to a systemic inflammatory response and coagulopathy [29]. Direct damage to endothelial cells by virus or indirect damage by immune cells, cytokines, free radicals, and imbalance between nitric oxide and activation of inflammatory cascades can lead to severe endothelial dysfunction, resulting in impaired microcirculation, vasoconstriction and organ ischemia, inflammation and tissue edema, and procoagulation [26, 30]. Destruction, disruption of endothelial intercellular junctions, cell swelling, and loss of contact with the basement membrane were found in the vascular walls of organs of patients with COVID-19. Various mechanisms, such as apoptosis, necrosis, or pyroptosis, may be responsible for these changes [31].

Endothelial dysfunction in the lungs impedes gas exchange across the alveolar-capillary membrane in patients after COVID-19 [24, 26]. Endothelial cell damage is often the initial site of thrombosis. In the early stages, endothelial cell activation is invisible, but they are the vulnerable basis of Long-COVID. The initial response to the destruction of the alveolar-capillary barrier is edematous infiltration in the alveoli and interstitial lining. After that, proliferation occurs as the alveolar barrier is restored by removing exudate [12]. However, prolonged inflammation, mediated, in particular, by P-selectin, is accompanied by damage to the alveolar-capillary membrane and impaired lung tissue regeneration, and can lead to the development of interstitial lung disease (ILD) [12, 17]. This is a heterogeneous group of diseases characterized by diffuse damage to the lung parenchyma and manifested by the development of a restrictive type of ventilatory disorders. A characteristic pathomorphologic feature of ILD is the development of fibrosis of varying degrees, which leads to restriction of lung tissue mobility, impaired ventilation and diffusion of gases through the alveolar-capillary membrane [7, 32]. Overexpression of transforming growth factor beta (TGF-β1) and other growth factors, such as fibroblast growth factor (FGF) and epidermal growth factor (EGF), activates profibrotic signaling pathways and contributes to an imbalance of the renin-angiotensin system and the development of post-COVID pulmonary fibrosis [17]. The mechanisms of fibrosis development are associated with a prolonged inflammatory response, damage to alveolar tissue, and impaired reparative processes. Persistent microthrombi in the lungs further complicate the course of the disease and can lead to irreversible changes in lung tissue [6, 33, 34]. The highest risk of developing fibrosis is among the elderly who have suffered severe forms of COVID-19, but it is also observed in patients with moderate severity [17].

Krebs von den Lungen-6 (KL-6), a high molecular weight mucin expressed on the surface of type II pneumocytes, is a promising biomarker for the diagnosis and monitoring of lung diseases, including post-covid fibrosis. Increased levels of KL-6 in the blood serum reflect damage to the alveolar-capillary barrier and can be used to assess the severity of the disease and predict its course [6].

One of the signs of damage to the alveolar-capillary membrane is residual alveolar consolidation in the form of “frosted glass” without signs of fibrosis. Histologic examination of the consolidation foci indicated significant infiltration of the alveolar tissue with T and B lymphocytes. Immunoproteomic analysis of bronchoalveolar lavage confirmed an increased number of cytotoxic lymphocytes, which correlated with epithelial damage, apoptosis, and

impaired tissue regeneration [33]. In addition, an increased number of cytotoxic lymphocytes in the bronchoalveolar lavage was associated with a decrease in lung diffusion capacity and objective measures of external respiratory function (Forced Vital Capacity (FVC) and Forced Expiratory Volume in one second (FEV1)) [12].

Patients with Long-COVID also had a diffuse increase in pulmonary vascularization with signs of vasodilation and vascular deformation. These changes indicate a violation of angiogenesis. Abnormal vascular development, in particular invasive angiogenesis and bronchopulmonary anastomoses, persist after recovery and may contribute to the development of chronic hypoxia. Studies of microcirculation have shown persistent thinning of the capillary network and persistence of microthrombi in patients with post-COVID syndrome, which leads to impaired ventilation-perfusion ratios and contributes to the development of chronic hypoxia [12, 33].

Also, in Long-COVID, diffuse neutrophilic infiltration of the lung tissue is observed, which often progresses to necrotizing capillaryitis, leading to a violation of the integrity of the alveolar-capillary barrier and the development of hemosiderosis [35].

Autopsies of patients who died as a result of COVID-19 complications revealed progressive diffuse alveolar damage, as well as significant pulmonary thrombosis. It is believed that endothelial dysfunction is a critical component of the pathogenesis of acute pulmonary dysfunction, such as progressive hypoxic respiratory failure and acute respiratory distress syndrome [16].

In case of endothelial dysfunction, the endothelium induces platelet aggregation and leukocyte recruitment to the site of injury [25]. ECs release vWF, angiopoietin-2 (Ang-2), P-selectin, and coagulation factor VIII. The presence of fibrinoid microclots and numerous inflammatory molecules in the soluble part of the blood indicates thrombotic endotheliitis as a key pathological process in Long-COVID. These fibrinolysis-resistant microclots contain numerous inflammatory molecules, including alpha-2-antiplasmin (α2AP), various fibrinogen chains, vWF, platelet factor 4 (PF4), and serum amyloid A (SAA) [37-39].

Tendencies toward endothelial cell apoptosis in Long-COVID are observed several months after the initial COVID-19 infection, which leads to impaired intercellular signal transduction between membrane proteins in these cells and vascular smooth muscle cells [38]. The EC glycocalyx contains the protein syndecan-1 (SDC-1). Once the glycocalyx destruction begins, the release of SDC-1 into the bloodstream can be a marker of endothelial dysfunction [33, 36, 40].

Also, there is a significant increase in the levels of soluble endothelial biomarkers, in particular sICAM-1, sVCAM-1 and sE-selectin, which are markers of endothelial inflammation [7, 29].

vWF plays a crucial role in platelet adhesion and aggregation at vascular injury sites, as well as in the stabilization of coagulation factor VIII, which are important processes for both hemostasis and thrombosis [22]. First, vWF is able to bind to platelet receptors and thus modulate platelet adhesion and aggregation. Secondly, pathological vWF multimers are responsible for thrombotic microangiopathy, play a role in the pathogenesis of microcirculatory occlusion, as well as impaired endothelial function, which leads to thrombotic and microvascular complications [38, 41]. The results of the study indicate that increased vWF expression in the pulmonary endothelium is an independent risk factor for the development of pulmonary embolism in patients with a long course of the disease [38]. It is also noted that high levels of vWF in patients with Long-COVID persist up to 1 year after acute infection, indicating a state of hypercoagulation [8].

In addition, P-selectin, which is a transmembrane glycoprotein and belongs to the selectin family, is expressed on the surface of activated platelets and endothelial cells. It facilitates the movement of leukocytes to the endothelium, promoting their migration to inflamed tissues [42]. It also promotes platelet aggregation and blood clot formation, which is an important component of hemostasis. In patients with Long-COVID, increased expression of P-selectin was found, which positively correlated with increased platelet activation and increased leukocyte adhesion [43].

Another such marker is endothelin-1 (ET-1). Endothelin is a vasoconstrictor consisting of 21 amino acids, represented by three isoforms, where ET-1 is the most studied [2]. Its secretion is regulated by various biological mediators. Angiotensin II, inflammatory cytokines, and oxidative stress induced by free radicals stimulate the release of ET-1. In contrast, nitric oxide, prostacyclin, and cyclic guanosine monophosphate (cGMP) inhibit its secretion [25]. High concentrations of ET-1 are observed in acute lung injury, primary pulmonary hypertension, sepsis, coronary heart disease, and diabetes [2, 36]. Also, its increase correlates with patient admission to the intensive care unit and severe symptoms [40, 42]. ET-1 regulation in patients with Long-COVID was found to be impaired within 8 months after mild to moderate COVID-19 [2, 44].

Six months after COVID-19 with acute respiratory distress syndrome, 30 % of patients had a decrease in lung diffusing capacity and dyspnea during exercise. During this period, plasma levels of biomarkers of endothelial dysfunction were elevated, namely: Angiopoietin-1 (Ang-1), Angiopoietin-2 (Ang-2), P-selectin, Intercellular adhesion molecule 1 (ICAM-1), and Vascular endothelial growth factor (VEGF); the combination of these proteins can affect the

pulmonary function of the vascular endothelium [7, 8, 37]. The analysis of the data obtained suggests that sICAM-1 and sVCAM-1 are more specific markers of long-term pulmonary endothelial dysfunction compared to Ang-2. Although Ang-2 may also be involved in the pathogenesis of Long-COVID, its role in the long-term consequences for pulmonary function, according to the literature, is less pronounced [8].

Conclusions

An important role in the development of lung damage in Long-COVID is played by endothelial dysfunction, which develops as a result of direct viral exposure to SARS-CoV-2 or persistent inflammatory reactions.

Endothelial cell dysfunction induces morphological and functional changes in the alveolar-capillary membrane. As a result, interstitial lung diseases develop, characterized by fibrosis, impaired diffusion and residual alveolar consolidation. Microcirculatory disorders caused by vasodilation and vascular deformation impair tissue oxygenation.

Elevated levels of biomarkers of endothelial dysfunction, such as Ang-1, Ang-2, vWF, P-selectin, ICAM-1, and VEGF, confirm active inflammation and endothelial dysfunction. Among them, sICAM-1 and sVCAM-1 have the highest association with decreased DLCO, indicating their potential role in the pathogenesis and progression of post-COVID pulmonary complications.

KL-6 is also an important biomarker of alveolar-capillary barrier damage, and its increase can be used to assess the risk of pulmonary fibrosis.

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ЕНДОТЕЛІАЛЬНА ДИСФУНКЦІЯ ТА УРАЖЕННЯ ЛЕГЕНЬ ПРИ LONG-COVID

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РЕЗЮМЕ. Проаналізовано сучасні дані наукових досліджень щодо ролі ендотеліальної дисфункції у патогенезі Long-COVID, зокрема, досліджено її вплив на альвеоло-капілярну мембрану та розвиток легеневих ускладнень. Оцінено потенціал біомаркерів ендотеліальної дисфункції для діагностики, прогнозування та розробки нових терапевтичних стратегій.

Аналіз відкритих наукових даних довів, що ендотеліальна дисфункція, спричинена SARS-CoV-2, була ключовим фактором розвитку Long-COVID, та призвела до змін у альвеоло-капілярній мембрані. У результаті цього ініціювався розвиток інтерстиційних захворювань легень із фіброзом, порушенням дифузії та мікроциркуляції, що призвело до погіршення оксигенації тканин. Встановлено ключову роль порушень ендотеліальної функції та стану альвеолярного епітелію, що відображаються у змінах рівнів Ang-1, Ang-2, vWF, P-селектину, ICAM-1, VEGF та KL-6 у розвитку та ступеню тяжкості легеневих ускладнень у пацієнтів із постковідним синдромом.

Це дослідження розширює науково-практичні знання фахівців у галузі медицини щодо ролі біомаркерів ендотеліальної дисфункції у розвитку легеневих ускладнень, асоційованих з Long-COVID, та демонструє їхній потенціал для діагностики, прогнозування та розробки нових терапевтичних стратегій.

Ключові слова: *Long-COVID, COVID-19, ендотеліальна дисфункція, біологічні маркери, дихальна система, міцне здоров'я.*

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