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Review

Pathogenetic mechanisms of dry eye syndrome in a novel coronavirus infection caused by SARS-CoV-2

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Abstract: The goal of this review was to analyze current knowledge on dry eye disease pathogenesis in a novel coronavirus infection (COVID-19) caused by SARS-CoV-2. Arguments are presented in favor of several possible pathogenic mechanisms of the disease development: inflammation and/or microcirculatory disorders aggravated by exposure to electromagnetic radiation of personal computers and by use of personal protective equipment.

Keywords: dry eye syndrome, COVID-19, cytokine storm, disseminated intravascular coagulation, laser Doppler flowmetry.

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At the end of 2019, a new severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) has appeared. The clinical spectrum of COVID-19 varies from asymptomatic infection or mild self-limited constitutional symptoms to a hyperinflammatory state (the so-called cytokine storm) with subsequent acute respiratory distress syndrome and lethal outcome [1-3].

SARS-CoV-2 is characterized by high virulence and pronounced tropism of various tissues. This correlates with key mutations in the receptor-binding domain that mediates direct contact with the cellular receptor of angiotensin-converting enzyme-2 (ACE-2) [4]. It is well known that the virus predominantly spreads by airborne transmission route [5, 6]. Common symptoms of infection include hyperthermia, dry cough, shortness of breath, and fatigue. Other clinical signs have been reported, such as gastrointestinal tract dysfunctions [7, 8] and ocular surface disorder – dry eye syndrome (DES) [9, 10].

It should be noted that DES development may even precede the onset of respiratory symptoms [11-13].

Due to the SARS-CoV-2 surface spike glycoprotein [14], the virus in the biological fluid binds with the ACE-2 receptors located on the corneal and conjunctival surface, thereby providing infection with potential site of entry [15-17], which may lead to ocular surface damage and further viral replication [18, 19]. This is evidenced by virus detection in the tear fluid and by polymerase chain reaction (real-time PCR) testing of lower eyelid conjunctival scrapping in patients with positive test results for COVID-19. The meta-analysis conducted by N. Nasiri et al. demonstrated that the organ of vision is involved in the pathological process in 11.03% of patients (95% CI: 5.71-17.72). Most often, patients are presented with dry eye symptoms, and/or foreign body sensation (16%), red eyes (13.3%), lacrimation (12.8%), itching (12.6%), eye pain (9.6%). %), and discharge (8.8%). Approximately one in ten COVID-19 patients develops at least one ocular symptom. Conjunctivitis had the highest prevalence among patients with confirmed COVID-19 (88.8%) [20, 21]. Clinical manifestation of SARS-CoV-associated ocular surface damage includes severe injection, chemosis, follicular conjunctivitis, phlyctena on the bulbar conjunctiva, and mild corneal epithelial edema [22-24].

The mechanism of the damaging effect of the virus on the eye tissue is not fully understood yet. A possible explanation is the direct damaging effect of virions, as well as inflammation activated by the immune system, which triggers compensatory and regenerative processes leading to the cytokine release syndrome (cytokine storm) [25]. The term *cytokine storm* was first introduced in 1993 to describe graft-versus-host disease and similar processes of rapid cytokine releases associated with autoimmune hemophagocytic lymphohistiocytosis, sepsis, cancer, acute immunotherapeutic responses, and infectious diseases [26]. It is now well established by numerous published studies what causes the inflammatory response cascade. An immune system dysregulation (activation of immune cells via Toll-like receptors – TLR, reduced anti-inflammatory response, etc.) is among major hypotheses on its origin. Activation of immune responses leads to enlarged cytokines levels (IL-6, IL-1β, IL-10, TNF-α, GM-CSF, IP-10, IFN-induced protein-10, IL-17, MCP-3, IL-1RA, etc.), which causes severe inflammatory responses in various body tissues [27-29].

Local and systemic cytokine responses are an integral part of the primary response to infection. In this case, the process of antibody-dependent cellular cytotoxicity is triggered, regulating the activity of cellular and humoral immune response and cytokine secretion by NK-cells (natural killer cells), macrophages, granulocytes, etc. [30]. Cytokines, such as interferon-α/β (IFN-α/β) and interleukin-1β (IL-1β), produced by epithelial cells, enable adjacent cell protection via expression of genes encoding IFN, while simultaneously activating immunocompetent NK-cells, which increases lytic potential of NK cells and stimulates the secretion of IFN–γ [31]. High levels of activated TNF-α, IL-12, and IL-6 lead to

hyperstimulation of NK cells [32]. With the development of the disease, T-cell responses induce additional production of cytokines against viral cytotoxicity, which results in addition of TLR ligands [33].

With SARS-CoV-2 infection in the blood serum, a high level of cytokines (IL-1β, IL-6, IL-8, IL-10, IFN-γ, and TNF-α) was determined [34]. Same cytokines were detected in the tear fluid via multiplex ligation-dependent probe amplification (MLPA) and enzyme-linked immunosorbent assay (ELISA) methods [35]. These findings reinforce the hypothesis on the pathogenetic mechanism of DES development based on the inflammatory process due to the presence of high content of proinflammatory cytokines (IL-1β, IL-6, IL-8, IL-10, IFN-γ, and TNF-α) in the tear fluid [36-40]. It was previously observed that SARS-CoV-2 contributes to the progression of DES manifestation. A cytokine storm occurs more often with more severe course of the SARS-CoV-2 disease, leading to the ocular surface damage [41-44]. It was estimated that IL-1β, IL-6, IL-8, IL-10, IFN-γ, and TNF-α were also represented and involved in coagulation cascade [45-48].

The presented *Figure* 1 demonstrates the development of coagulopathy in COVID-19 infection. Activation of mononuclear cells results in a procoagulant response, in which abnormal fibrin deposition and an increase in the incidence of venous thromboembolism occur. SARS-CoV-2 also causes endothelial damage, which is succeeded by release of plasminogen activators, which, in combination with a procoagulant reaction, elevates serum D-dimer, C-reactive protein, ferritin, and procalcitonin levels [49–52]. The simultaneous release of high-molecular-weight multimers of von Willebrand factor leads to thrombosis in the organs and tissues, including blood vessels in the eye [53].

These pathophysiological mechanisms contribute to disseminated intravascular coagulation (DIC), which occurs in over 70% of patients with SARS-CoV-2 infection [54, 55]. Besides hypercoagulation associated with DIC, activation of blood plasma coagulation pathway, intravascular aggregation of platelets and other blood cells, and microcirculation disorders in various organs are present. As a result, a morphological blockade of the bloodstream by fibrin masses and cell aggregates is formed which leads to ischemia and tissue hypoxia [56-58]. The same pathogenetic mechanism underlies DES development in the case of vasculitis associated with systemic diseases [59].

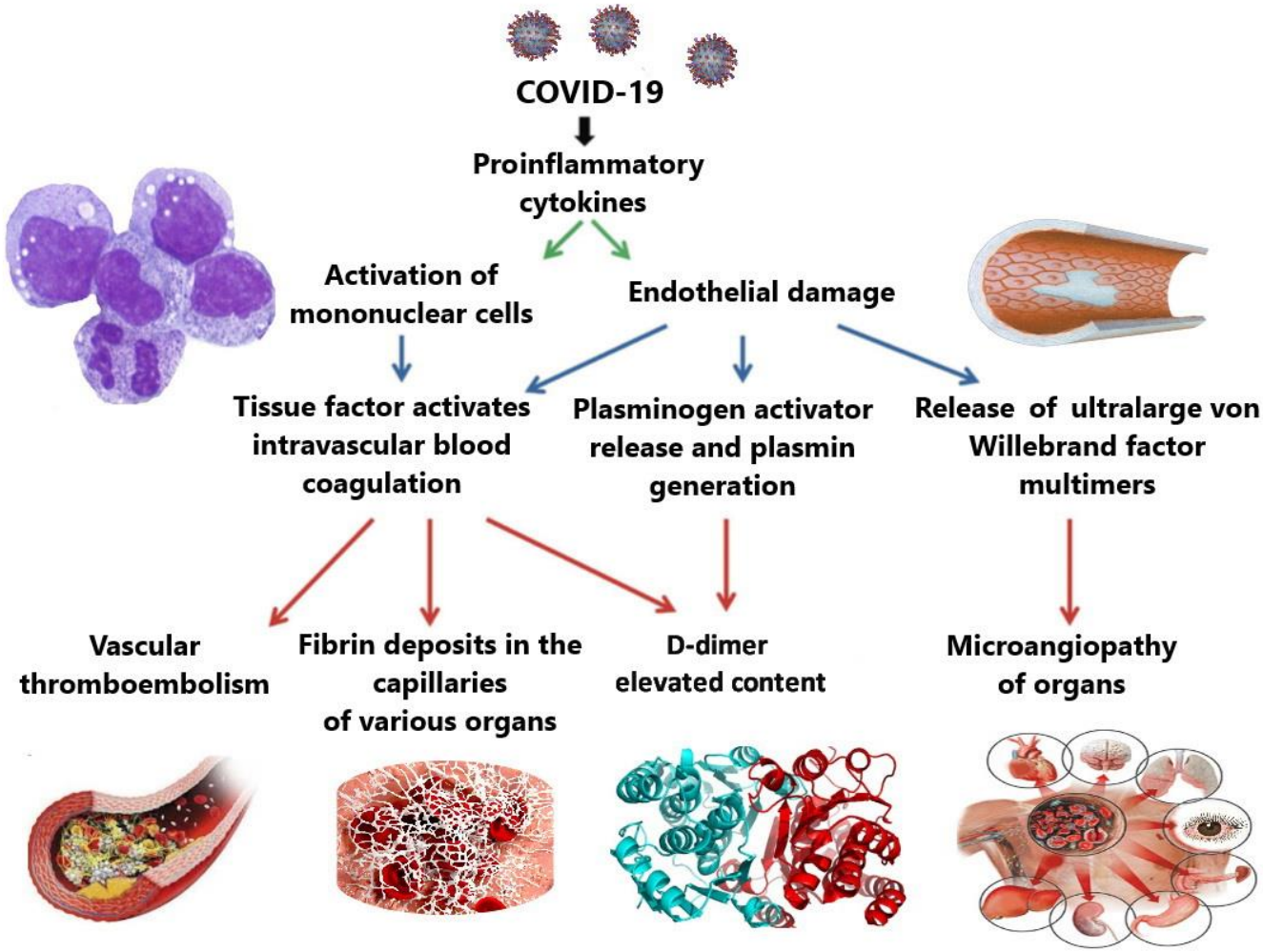

Figure 1. Schematic representation of the pathogenesis of COVID-19 coagulopathy caused by the SARS-CoV-2

The vessels of the bulbar conjunctiva are the most accessible for visualization to analyze the microcirculatory bloodstream in arterioles, venules, and capillaries located in the conjunctival superficial layers. It is well known that the conjunctiva receives its blood supply from two sources: the superior and inferior arterial arches of the eyelids, which are formed of the lacrimal and anterior ethmoidal arteries, and the anterior ciliary arteries, which originate from the muscular branches. The external carotid artery also partly supplies blood to the bulbar conjunctiva vascular system. There are several vascular layers in the conjunctiva: superficial (subepithelial), middle (subconjunctival), and deep (episcleral). The highest density of capillaries is observed in the eyelids parallel to the conjunctival folds [60]. It is important to analyze the changes in microvasculature due to its significant role in the process of lacrimation: some components of the tear fluid are provided immediately from the microvasculature. Disorder in microvasculature, caused by SARS-CoV-2, may result in qualitative and quantitative disorders of tear fluid composition.

Several methods may provide an objective assessment of the state of the conjunctival microvascular network.

L. MacKenzie et al., conducted a study of saturation of conjunctival vessels using the principle of retinal oximetry. Their results showed a decrease in hemoglobin saturation with oxygen in the conjunctival and episcleral vessels under conditions of mild hypoxia. In these circumstances, episcleral vessels expand, while conjunctival vessels do not undergo significant changes due to rapid reoxygenation and oxygen diffusion from the environment [61].

Some authors proposed a method for assessing oxygenation in the microcirculatory bloodstream of the anterior eye segment (palpebral and bulbar conjunctiva): diffuse reflectance spectroscopy, utilizing visible light. This method allows determining blood oxygenation from a series of multispectral images obtained with band-pass filters, based on the absorption spectrum of hemoglobin wavelengths, which provides an objective assessment of vascular bloodstream in the ocular anterior segment [62].

Video biomicroscopy of the bulbar conjunctiva allows visualizing all anatomical parts of the microvasculature (arterioles, venules, capillaries, arterio-venous anastomoses) and to assess vascular permeability, interstitial space, and rheological properties of microcirculatory bloodstream [63].

Another method to assess conjunctival blood and lymph flow is the method of laser Doppler flowmetry (LDF) conducted with LASMA MC-1 peripheral blood flow and lymph flow analyzer. LDF is a non-invasive diagnostic method based on optical laser probing of tissues and analysis of the scattered reflected signal induced by moving erythrocytes. The analyzer filters the frequency spectra of the Doppler shift of laser radiation scattered from erythrocytes in the microvasculature, and scatterers from lymph formation in the lymphatic vessels in the speed ranges corresponding to their movement. Laser radiation reflected from static (stationary) tissue components does not change its frequency, while reflected radiation from moving particles (erythrocytes) has a Doppler frequency shift relative to the probing signal. The variable component of the reflected signal is determined by two factors: the concentration of erythrocytes in the test sample and the speed of their movement. This method has high specificity and high sensitivity and allows determining the parameters of microcirculation and lymph flow, such as the coefficient of variation, and neurogenic and myogenic fluctuations [63, 64].

Previously conducted studies recognized the role played by two more factors, which may also contribute to the onset and/or progression of DES in SARS-CoV-2 infection.

One of them is electromagnetic radiation, which is a risk factor for the development of DES due to frequent and prolonged use of personal computers and mobile devices during distance learning or remote work [65]. Blinking frequency decreases to an average of 4-5 times per minute, compared with reference value of up to 15, which leads to excessive evaporation of the tear fluid and precorneal tear film instability. Ultimately, this leads to xerotic changes in the cornea and conjunctiva.

Another triggering factor of DES, associated with SARS-CoV-2, is an extensive use of personal protective equipment (masks, respirators). Improper and prolonged wearing of masks/respirators causes an uneven distribution of exhaled warm air and increase in the evaporation of tear fluid from the ocular surface [66]. This mechanism of DES development is similar to the mechanism underlying constant positive airway pressure (CPAP) therapy, which results in augmented tear evaporation, eye irritation, and squamous metaplasia of the conjunctiva [67].

Collectively, clinical experience to date suggests that COVID-19 infection with SARS-CoV-2 results in ocular surface damage or progression of DES. However, studies of eye damage in patients with SARS-CoV-2 mainly involve the description of the clinical manifestations of the disease. Currently, there are no data on an objective assessment of the ocular surface lesion and its severity and reversibility.

The existing body of research suggests that the mechanism of DES development in SARS-CoV-2 infection is probably associated with the activation of one or two pathways of pathogenesis: inflammation and/or microcirculatory disorders complicated by exposure to electromagnetic radiation from personal computers and the use of personal protective equipment. There are concerns about protective measures during the COVID-19 pandemic and how they could lead to an increase in the number of patients with ocular surface disease. Thus, further studies are needed to determine the components of the pathogenesis of DES in the case of SARS-CoV-2 infection.

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