



Endothelial dysfunction as a consequence of COVID-19

Disfunción endotelial como consecuencia de COVID-19

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ABSTRACT. COVID-19 (coronavirus infectious disease 2019) is caused by the virus SARS-CoV-2 and it has been a major health public problem worldwide, with complications and more than a million deaths around the world. The virus is part of the *Coronaviridae* family, and beta coronavirus (β -CoV) genus. Possess several proteins that codify the RNA and take action in the pathogenesis of the diseases. COVID-19 can occur as an asymptomatic disease or with symptoms like cough, shortness of breath, fever, pneumonia, pulmonary edema, severe acute respiratory syndrome (SARS), in some cases neurological and gastrointestinal symptoms, even death. SARS-CoV-2 has several manifestations, in this review, we collect information for most recent articles about gastrointestinal manifestations, endothelial function, and the molecules involved in it, likewise, sepsis and inflammatory disease, and how the virus can act in that disease. SARS-CoV-2 causes endothelial dysfunction by infection and replication in the endothelial cells, additionally, by inflammatory interleukins release. Such as sepsis SARS-CoV-2 causes coagulopathy disorders; platelet aggregation, micro thrombosis, and severe complications, showing in a dimer D increased, and prothrombin time prolongation. Therefore, the aim of this article is to collect recent information available about the effect of SARS-CoV-2 on different organs, mainly gastrointestinal and endothelial function.

Keywords: SARS-CoV-2, COVID-19, endothelial dysfunction, thrombosis, coagulation disorders.

INTRODUCTION

COVID-19 (coronavirus infectious disease 2019) is caused by the virus SARS-CoV-2 and it has been a major health public problem worldwide with complications, and more than 500,000 deaths around the world. The virus is part

RESUMEN. La COVID-19 (*coronavirus infectious disease 2019*) es una enfermedad causada por el virus SARS-CoV-2 y ha sido un problema de salud a nivel mundial, con mayor morbilidad y mortalidad. El virus pertenece a la familia *Coronaviridae*, perteneciente del género betacoronavirus. (β -CoV). Posee proteínas específicas que codifican el RNA viral y toman acción en la patogénesis de la enfermedad. La COVID-19 puede cursar de manera asintomática o presentar los siguientes síntomas: tos, disnea, fiebre, neumonía, edema pulmonar, síndrome de insuficiencia respiratoria aguda (SIRA), en algunos casos síntomas gastrointestinales, neurológicos, incluso la muerte. El virus SARS-CoV-2 tiene diferentes manifestaciones a nivel sistémico, en este artículo se recopila la más reciente información sobre las manifestaciones gastrointestinales, función endotelial y sus moléculas, así como la relación entre el SARS-CoV-2 y la enfermedad inflamatoria y sepsis. El SARS-CoV-2 afecta al endotelio a través de la infección y replicación en las células endoteliales, además de generar una liberación de interleucinas inflamatorias. Así como la sepsis, el virus puede causar trastornos de la coagulación como agregación plaquetaria, microtrombosis y complicaciones más severas, demostradas en el incremento en el dímero D, y tiempos de coagulación prolongados. El objetivo de este estudio es resumir la información actual disponible acerca del SARS-CoV-2 en diferentes órganos y la función endotelial.

Palabras clave: SARS-CoV-2, COVID-19, disfunción endotelial, trombosis, alteraciones de la coagulación.

of the *Coronaviridae* family, and beta coronavirus (β -CoV) genus, possesses several proteins that codify the RNA and takes action in the pathogenesis of the diseases.¹

The pathogenesis of the virus depends on the receptor angiotensin-converting enzyme 2 (ACE2), a cell surface receptor that is present in a greater proportion in the lung and small intestine. The S protein is responsible for binding with ACE2 through the transmembrane protease receptor serine (TMPRSS), mainly in type 2 pneumocytes. The estimation of the COVID-19 incubation period is from 1 to 14 days from the first contact to the onset of symptoms.²

SARS-CoV-2 can occur as an asymptomatic disease or with symptoms like cough, shortness of breath, fever, pneumonia pulmonary edema, severe acute respiratory syndrome (SARS), and in some cases neurological and gastrointestinal symptoms³ even death.¹

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SARS-CoV-2 and gastrointestinal system

SARS-CoV-2 can infect the cells of the gastrointestinal system due to the high proportion of ACE receptors and TMPRSS 2 in the esophagus, liver, and colon. It has been noticed a relationship between the expression of amino-acid transporters in the small bowel, and ACE2, this abnormality is related to enteritis and the loss of important amino acids in the human body.⁴

For the attachment of the virus into the cell membrane and the ACE2 receptor, it needs to break up into two parts (S1 and S2), this split is made by the serine protease, facilitating the endocytosis. Bound to the ACE2 receptor, there is an amino acid transporter BOAT1, when the SARS-CoV-2 blockage the membrane receptor ACE2, also block the BOAT1, reducing the transport of amino acids like tryptophan, which is important for the production of the antimicrobial peptide, likewise, citrulline malabsorption, which is important for the endothelial function.⁵

An altered intestinal microbiome combined with inflammation, increased the intestinal permeability, allowing toxin and bacterial translocation to the systemic circulation, this can contribute to multiorgan dysfunction.⁶

In some studies of mice infected by SARS-CoV, there have been such manifestations of GI tract damage, especially in the small bowel with enterocyte desquamation, edema, lymphocyte infiltration, and small vessel dilatation, also severe hemorrhage in the mesenteric ganglia and necrosis.^{5,6}

Once the virus is in several organs, type II pneumocyte, endothelial cells, smooth muscle, macrophages, leads to inflammation by overproduction of pro-inflammatory cytokines, macrophages recruitment, and pro-inflammatory granulocytes producing a cytokine storm, endothelial dysfunction, microthrombi, small pulmonary vessel obstruction, vascular tone modification and thrombosis in several vascular territories.⁴ The virus is easily spreading through several organs, one of the most important organs in which acts is the endothelial function.

Endothelial function

The endothelial cells are the main component of the blood vessels internal layer, it works to maintain the separation between the bloodstream and the extravascular tissues.⁷ Endothelia is the main regulator of vascular homeostasis, the balance between vasoconstriction and vasodilatation, inhibits the proliferation/migration of the vascular smooth muscle cell, also modulates the hemostasia.⁸

Endothelial dysfunction can cause a lower expression of vasodilatory and antithrombic molecules; this is one of the characteristics associated with SARS-CoV-2 and the altered endothelial cell membranes. Additionally,

generalized vasculopathy microangiopathy thrombosis and alveolar-capillary occlusion have been found in the lungs of COVID-19 patients.⁹

Microvascular and macrovascular severe dysfunction combined with immune overreaction can disrupt the atherosclerotic plaques and induce ischemic events, such as acute coronary syndrome.^{2,8}

The main component for the vasodilatation in the endothelium is made by the action of nitric oxide (NO), thorough the precursor L-arginine catalyzed by endothelial nitric oxide synthase (eNOS), resulting in nitric oxide and L-citrulline.⁸

L-citrulline

L-citrulline is a natural precursor for L-arginine helping to *de novo* synthesis of it. It is an amino acid product from the metabolism of glutamine. At the same time, it can help to greater the production of nitric oxide.¹⁰

It is effective in cardiovascular function associated with endothelial function, such as hypertension, heart failure, atherosclerosis, diabetic vascular disease, and ischemic-reperfusion injury. One of the differences with L-arginine is that L-citrulline is not metabolized by the intestine either the liver and it does not induce the tissular arginase, on the contrary, inhibits its activity. Another characteristic of L-citrulline is its metabolism in the kidney, which also can transform into L-arginine increasing the plasmatic and tissular levels of L-arginine.¹⁰

It has been shown that L-citrulline has shown promise to be a good intervention to reduce the arterial tension (both at rest and induced by stress) in adults with pre and hypertension, also with experimental evidence, it can protect against atherogenic endothelial damage.¹¹

Sepsis, inflammatory disease and their relationship with endothelial function

Inflammatory disease and sepsis are characterized by organic dysfunction, as a consequence of poor blood flow and a low vascular peripheric resistance, particularly at the microcirculatory site, resulting in inflammation and endotoxemia. Likewise, there is an association between sepsis and a reduction in the L-arginine levels, turns it over into a semi-essential amino-acid during stress condition such as sepsis.¹²

It has been shown that IL-6 plays an important role by suppressing the endothelial nitric oxide synthase (eNOS) function and induce the expression of tissular mononuclear cellular factor, as a result, the activation of the coagulation pathway and thrombin production.¹³

In an experimental study with sepsis-induced in Wistar rats, it was shown that the administration of

L-citrulline reduces the IL-6 levels, suggesting that it can help to increase the nitric oxide production; promoting microvascular dilatation and as a consequence, avoiding the tissular hypoxia and diminishing the intravascular coagulation activation.¹⁴

In another study with L-arginine and L-citrulline supplementation over the endothelial function of children and adolescent with mitochondrial diseases; L-arginine or L-citrulline were administered depending on the weight (500 mg/kg/day, in < 20 kg and 10 g/m² body surface area, distributed in three doses, respectively), in both groups, it was shown an increase in reactive hyperemia, therefore, an improved over the endothelial function.¹⁵

An interesting point is the fact that the endothelial cells of the lung arteries do not express the enzymes required for the production *de novo* of L-citrulline, therefore the intracellular concentration depends on the L-citrulline circulating. There is limited information about L-citrulline carriers on the pulmonary endothelial cells.¹⁶

Sodium natural amino acid transporters (SNAT) are one of the responsible systems of neutral amino acid transport. Due to the potential role over the L-citrulline transporter, it can evaluate the expression of SNAT on lungs, pulmonary arteries, and pulmonary arteries endothelial cells (PAEC) of newborn piglets.¹⁶⁻¹⁸ The main SNAT expression founded over pulmonary arteries and lungs in those piglets were the SNAT 1, 2, 3, and 5.

Dikalova evaluates the function of SNAT1 over the PAECs newborn piglets and they found that hypoxic *in vitro* increases the absorption of L-citrulline; SNAT1 was identified as a responsible transporter of L-citrulline over hypoxic PAEC and their disposal. Likewise, SNAT1 silences the RNA, reduces basal nitric oxide production, and prevents the L-citrulline-induced elevations in NO productions in both normoxic and hypoxic PAECs. Those findings suggest that an increase in the SNAT1 and a major transport of citrulline can participate in the NO signaling during chronic pulmonary hypertension induced by hypoxia.^{16,17,19}

In newborn piglets model with induced pulmonary hypertension show that L-citrulline treatment increases the production of pulmonary vascular NO, and decreases the elevation of vascular resistance pulmonary.¹⁸

Also, there have been found that the L-citrulline in a subcutaneous administration improves the pulmonary vasculature remodeling, and reduces the right ventricular hypertrophy, those cardiovascular abnormalities are associated with pulmonary hypertension. This could suggest that the use of L-citrulline can be used in humans with a high risk for developing pulmonary hypertension.^{16,20}

In humans, it has been shown an improvement over the left ventricular ejection fraction, functional class, and endothelial function evaluated by photoplethysmography after four months of L-citrulline treatment. Moreover,

it has been found an improvement in endothelial function in diastolic heart failure patients with 60 days of treatment.²¹ Another study with obesity and hypertension or pre-hypertension found a reduction over the ankle blood pressure (endothelial function) and carotid augmentation index with watermelon extract supplementation as the main source of L-citrulline after six weeks of it.²²

There are biomarkers associated with endothelial dysfunction including proteases, vascular adhesion cellular molecule (VCAM), glycocalyx components, coagulation factors such as tissue factor, plasminogen activator inhibitor type 1 (PAI1). During inflammation, there is a release of integrins and selectins associated with endothelial cellular activation. Those biomarkers can be benchmarks for the development of sepsis.²³

In addition, the endothelial glycocalyx is a layer with a thickness from 1 to 3 μ m covering the luminal membrane. It has been associated with pathologies like sepsis and there has shown damage to it, with oxidants, hyperglycemic, cytokines, and bacterial endotoxins.²⁴

The glycocalyx detachment happened because of reactive oxygen species (ROS) as hydrogen peroxide, hydroxyl anions, and superoxide, heparinase and tumor necrosis factor also can participate in it. As a consequence, the endothelium increases the degradation products, and barrier function is lost, this is associated with edema, and contributes to organ failure induced by sepsis, it can be reverted with antioxidants like catalase and superoxide dismutase (SOD).²⁴

There have been evaluated other molecules like syndecan-1, heparan sulfate, heparinase, endocan, and angiopoietins, and they are used as a sepsis diagnosis tool. The levels of syndecan-1 have been associated with endothelial damage, and glycocalyx degradation. Steppan and cols. evaluates the levels of syndecan-1 in 104 patients with septic shock, 28 patients with abdominal surgery and 18 healthy volunteers. The syndecan-1 levels were extremely high in sepsis and surgery groups than in the healthy group.²⁵

Heparanase is a molecule associated with metastasis cases, also elevated in pulmonary and renal insufficiency with sepsis.²⁵

Endocan also called Endothelial cell-specific molecule-1 (ESM-1) is a soluble proteoglycan expressed during an inflammatory state and it has been shown as a biomarker of endothelial dysfunction in sepsis. Endocan was associated with severe sepsis and was significantly associated with 30 days and 6 months of mortality.²⁶

Endothelial function and COVID-19

One of the main characteristics of severe COVID-19 patients is the activation of the clotting pathway with

the possible development of disseminated intravascular coagulation (DIC). Also, linked to activation and dysfunction of the endothelial cells, as a consequence of the integrity of vascular loss and the endothelial cells death of the membrane cell, which is thrombogenic and activates the coagulation cascade.

The coagulation pathway is activated by interleukin-1 β and tumor necrosis factor (TNF) expressing selectin-P, Von Willebrand factor, and fibrinogen, binding with platelets. Moreover, endothelial cells release trophic cytokines increasing the platelet production and releasing vascular endothelial growth factor (VEGF), which acts over endothelial cells increasing tissue factor expression (principal activator of the coagulation cascade). As a response, the body organism develops several mechanisms to degrade the fibrin clots, this can explain the high levels of fibrin degradation products, which are associated with the worst prognosis.

As a whole, the small vessel congestion, DIC, and thrombosis over large arteries develop ischemic of the pulmonary tissue, unleash angiogenesis, and possible endothelial hyperplasia. The last one can help to exacerbate the mechanism of ischemia, nonetheless, angiogenesis can reduce it. The new vessels can promote inflammation by acting as ducts for inflammatory cells which are attracted by activated endothelial cells.²⁷

All of the above can contribute to pulmonary microvascular thrombosis, bronchoalveolar fibrin deposits (a characteristic of the acute distress syndrome of the adult), and thromboembolic complications with a massive release of Von Willebrand factor and plasminogen activator.²⁸

COVID-19 can disrupt the endothelial system, causing a massive release of von Willebrand factor (VWF), favoring thrombosis. The propagation of it is facilitated by the inflammation, the endothelial dysfunction which releases IL-6 as a response to the virus, amplifying the host immune response, causing the cytokines torment.²⁹ Although the vasculitis of the immune complex is part of the pathology of COVID-19, however, there is not enough evidence of it. The activation of the coagulation cascade on COVID-19 predisposed the coagulopathy induced by sepsis (CIS) and disseminated intravascular coagulopathy.²⁹

Also, COVID-19 was associated with hyperviscosity. According to Cheryl *et al.* with 15 patients with COVID-19 pneumonia diagnosis and admitted to the intensive care unit, they found that all patients exceed 95% of plasma viscosity and this hyperviscosity was correlated with sequential organ failure (SOFA). Hyperviscosity is not only associated with thrombosis, moreover, with endothelial damage and dysfunction.^{29,30}

Another hypothesis about the damage of COVID-19 is not only the macrovascular damage, moreover is focused on the microvascular and the NETs (tissue factor and neutrophil

extracellular traps), they predispose to thrombosis and one of their functions is to act as a scaffold for fibrin deposits. They have the potential to propagate inflammation and microvascular thrombosis, including the lungs of patients with acute respiratory syndrome. In 50 patients report with COVID-19, they show elevated levels of cell-free DNA, myeloperoxidase (MPO), and citrullinated histone H3 (cit-H3).^{31,32}

NETs can work as a nest of fibrin in addition to the platelet's accumulation. Furthermore, it has been shown that VWF *ex vivo* interacts with extracellular DNA providing a possible link between NET and platelet interaction.

Bin Cai *et cols.*, show a diminished in TNF-, IL-6, IL-1 β , over the first stages of sepsis, in Wistar rats with cecal ligation puncture and L-citrulline.³³

When TNF-amounts diminish, the leucocytes stimuli, and the endothelial cells for the inflammatory cytokines' pathway, are reduced too. As a consequence, the capacity to damage the glycocalyx also diminished and the platelet adhesion is favored by the p-selectin. L-citrulline can reduce IL-6 and it can help to reduce the micro thrombosis risk and the activity of the extrinsic pathway of coagulation.^{14,33}

CONCLUSION

SARS-CoV-2 causes endothelial dysfunction by infection and replication in the endothelial cells, additionally, by inflammatory interleukins release.

Such as sepsis SARS-CoV-2 causes coagulopathy disorders; platelet aggregation, micro thrombosis, and severe complications, showing in a dimer D increased, and prothrombin time prolongation, although, a certain amount of thrombocytopenic by consume.

Those patients with sepsis, it has been demonstrated some damage in other organs like the heart, kidney, bowel, affecting the abortion of amino acids, among these, L-citrulline and as a consequence the L-arginine plasmatic level.

The L-citrulline administration can improve endothelial function and reduces the thrombosis caused by COVID-19.

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