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COVID-19–Associated Endothelial Dysfunction and Microvascular Injury From Pathophysiology to Clinical Manifestations



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KEYWORDS

- Covid-19 clinical manifestations • Endothelial dysfunction • Systemic inflammation • ACE2
- ADAM17

KEY POINTS

- The broad spectrum of clinical manifestations, affecting almost all organs and systems, is a consequence of the endothelial dysfunction and systemic inflammatory response.
- Endothelial cells activated by a hyperinflammatory state induced by viral infection may promote localized inflammation, increase reactive oxidative species production, and alter dynamic interplay between the procoagulant and fibrinolytic factors in the vascular system, leading to thrombotic disease not only in the pulmonary circulation but also in peripheral veins and arteries.
- Several data support the involvement of an increased activity of ADAM17 in both COVID-19's comorbidities and SARS-CoV-2 infection. In fact, the ADAM17 upregulation leads to the angiotensin-converting enzyme 2 (ACE2) ectodomain proteolytic cleavage, facilitating viral entry, and to the cleavage of tumor necrosis factor alpha and interleukin-6 receptor and other proinflammatory molecules, contributing to the “cytokine storm” and reinforcing the inflammatory process during SARS-CoV-2 infection.
- The molecular interaction of SARS-CoV-2 with the ACE2 receptor located in the endothelial cell surface, either at the pulmonary and systemic level, leads to early impairment of endothelial function, which, in turn, is followed by vascular inflammation and thrombosis of peripheral blood vessels.

INTRODUCTION

Coronavirus-19 disease (COVID-19) affects more people than previous coronavirus infections, namely severe acute respiratory syndrome (SARS) and middle east respiratory syndrome (MERS) and has a higher mortality. Higher incidence and mortality can probably be explained by COVID-19 causative agent's greater affinity (about 10–20 times) for angiotensin-converting

enzyme 2 (ACE2) receptor compared with other coronaviruses.^{1,2} According to the World Health Organization's (WHO) recent data “there have been 199.466.211 confirmed cases of COVID-19, including 4.244.541 deaths” (source: WHO data, August 4, 2021). In the same way as SARS and MERS, it affects the respiratory system. Nevertheless, because of the viral rapid diffusion and the increased numbers of infected people, many extra respiratory system manifestations have been

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documented.^{3–5} Severe symptoms result from hyperinflammatory response, which in turn causes systemic cytokine release and endothelial damage, and several clinical and laboratory findings support the role of endothelial dysfunction in the pathophysiology of disease, suggesting that the endothelium may represent an attractive target for new treatments.⁶

In this review, the authors first summarize clinical manifestations, then present symptoms of COVID-19 and the pathophysiological mechanisms underlying specific organ/system disease. After, they review current understanding of key pathophysiological mechanisms with particular regard to the role of endothelial dysfunction, microvascular injury, and systemic inflammatory response in disease progression and severity. Finally, they illustrate possible novel mechanisms and treatments aimed at protecting the endothelium.

COVID-19 CLINICAL MANIFESTATIONS

COVID-19 transmission mainly occurs directly via respiratory and saliva droplets from person to person. Indirect transmission, through fomites, may also occur. Airborne transmission only occurs when procedures generate aerosol. Incubation period is usually less than 1 week (about 5–6 days) but may last longer up to 2 weeks. Initial symptoms are nonspecific and similarly to other virosis such as influenza: fatigue, myalgias, dry cough, and low-grade fever.⁷ Symptoms improve in most of the cases or progress to dyspnea in fewer ones.³ Zeng and colleagues reviewed the symptomatology of COVID-19: the commonest signs/symptoms were fever (90%) and cough (68%) followed by dyspnea (22%), headache (12%), and sore throat (14%). Diarrhea was present in only about 4% of patients. Mean duration of fever in survivors is about 12 days, whereas mean duration of cough is slightly longer (19 days).⁸ Although fever is a very common finding, its absence does not rule out the diagnosis.⁹ Longer duration of fever is proportionate to disease's severity (31 days for patients admitted to the intensive care unit vs 9 days for those hospitalized in a different setting)¹⁰. As mentioned earlier, in about one-fifth of patients disease progresses to dyspnea.^{3,7} Rapid progression to respiratory failure requiring noninvasive and invasive ventilation may occur. Viral respiratory invasion alone is insufficient to explain these findings. Endothelial dysfunction, subsequent inflammation, and lung injury with diffuse alveolar damage leading in some cases to acute distress respiratory syndrome is the underlying pathophysiological

mechanism responsible for respiratory failure.⁷ Patients may experience other clinical features that strongly suggest endothelial dysfunction and microvascular thrombosis. Pain, warmth, and localized limb swelling are consistent with deep venous thrombosis, and acute onset tachycardia, dyspnea, and chest pain strongly suggest pulmonary embolism.⁵

The alterations of the coagulation mechanisms observed in COVID-19 can lead to acute thrombotic phenomena of the arteries of the lower limbs, curiously even in patients with healthy arteries (ie, in the absence of underlying peripheral arterial disease) or without atrial fibrillation or preexisting coagulation disorders. The most severe acute ischemia occurs in patients admitted to intensive care units for severe forms of COVID-19 pneumonia: they rarely represent the only clinical manifestation of the infection. The conservative approach with medical therapy alone may be the most appropriate, considering the poor results of surgical revascularization. This latter, on the contrary, has always been characterized by excellent results in non-COVID patients operated on within a few hours of the onset of acute symptoms. The rate of limb loss/amputation is dramatically high in patients with COVID affected by acute limb ischemia.¹¹

Concomitant oliguria and general symptoms (ie, nausea and vomiting) deserve urgent renal function testing and raise the possibility of uremia in the setting of acute kidney injury. In addition, new-onset generalized edema reflects heart failure and/or heavy proteinuria. Moreover, the presence/absence of associated signs/symptoms may further contribute to orient the diagnosis during patient's physical examination. For instance, the coexistence of dyspnea, new-onset generalized edema with symmetric periorbital involvement, and negative hepatojugular reflux indicates concomitant respiratory and renal rather than cardiac involvement. Laboratory tests would eventually show abnormal renal function, hypoalbuminemia, and heavy proteinuria, and transthoracic echocardiography confirms normal systolic function and absence of valves abnormalities. Severe headache may reflect central venous thrombosis or intracerebral hemorrhage. Finally, systemic inflammatory response may indirectly cause neurologic signs/symptoms such as headache, encephalopathy, or seizures.⁵

COVID-19 is characterized by a wide spectrum of clinical severity. Asymptomatic persons experience no symptoms and have normal chest radiographs but play an important role in disease transmission to others. Mild illness is characterized by general symptoms common to other

virosis; gastrointestinal symptoms may be present too (abdominal pain, nausea, vomiting, and diarrhea). In moderate illness, symptoms of pneumonia are present with still normal blood gases, and interstitial ground-glass opacities appear on high-resolution computed tomography scan. Severe illness is characterized by pneumonia with hypoxemia (peripheral oxygen saturation is <92% in ambient air). Finally, critical state is characterized by the presence of acute distress respiratory syndrome, coagulation disorders, cardiac failure, acute renal injury, and shock.^{7,9,12–17} Patients with comorbidities have a worse disease course and prognosis compared with healthy ones, as observed in previous coronavirus infections.¹ Advanced age, male sex, diabetes, hypertension, ischemic heart disease, cancer, chronic obstructive pulmonary disease, and chronic renal insufficiency are risk factors for developing a severe form of COVID-19.^{18–20} These conditions affect negatively patient’s immune system.^{1,21}

A full description of the COVID-19 treatment by organ/system involvement is beyond the scope of this review. Most suitable treatment should be prescribed depending on disease’s severity and

organ involvement. At the present time, treatment encompasses oxygen (when required); symptomatic, antiinflammatory, antiviral, and anticoagulant drugs (prophylactic or therapeutic, with low-molecular-weight heparin); and monoclonal antibodies. Moreover, in selected patients resistant to treatment, plasma exchange therapy and immunomodulatory medications may be required.⁷ Updated COVID-19 treatment guidelines by disease’s severity are provided by national and international institutions at their Web sites. Finally, major concern has been raised about the use of renin-angiotensin blocking agents in patients with COVID-19. Routine discontinuation is not recommended by the guidelines of international cardiology societies.^{22,23}

A Molecular Perspective to Explain Endothelial Cell Activation in COVID 19

The COVID-19 clinical manifestations by organ/system and the underlying pathophysiological mechanisms of disease are summarized in **Tables 1–3**. Mechanisms that specifically contribute to determine a clinical manifestation are also

Table 1 COVID-19 clinical manifestations by system and pathophysiological mechanism	
Clinical Manifestations (Refs. 1–5)	Pathophysiological Mechanisms (Refs. 1–5)
<i>Respiratory</i> Pneumonia Acute respiratory distress syndrome Microvascular lung thrombosis Respiratory failure	<i>Multifactorial</i> Direct viral injury and inflammation Endothelial dysfunction • proinflammatory • procoagulant • proaggregating • capillary leakage • increased vascular permeability Systemic inflammatory response (“cytokine storm”)
<i>Cardiac</i> Myocarditis/pericarditis Arrhythmias Right or/and left heart failure Acute coronary syndrome Cardiogenic shock	<i>Multifactorial</i> Direct viral injury and inflammation Endothelial dysfunction • proinflammatory • procoagulant High ACE2 levels Systemic inflammatory response (“cytokine storm”) Hypoxemia Oxygen supply mismatch
<i>Arterial</i> Large vessel occlusion: clinical presentation depending on the affected artery (cerebral, cardiac, mesenteric, renal, limb) Central nervous system vasculitis	<i>Multifactorial</i> Direct viral injury Endothelial dysfunction • proinflammatory • procoagulant • proaggregating Hypoxia

Table 2 COVID-19 clinical manifestations by system and pathophysiological mechanism	
Clinical Manifestations (Refs. 1-5)	Pathophysiological Mechanisms (Refs. 1-5)
<p><i>Venous thromboembolism</i></p> <ul style="list-style-type: none"> Deep vein thrombosis Pulmonary embolism Intravenous/intraarterial catheters and extracorporeal circuit thrombosis Central venous thrombosis 	<p><i>Multifactorial</i></p> <ul style="list-style-type: none"> Endothelial dysfunction <ul style="list-style-type: none"> • proinflammatory • prooxidant • procoagulant • proaggregating Hypoxia
<p><i>Renal</i></p> <ul style="list-style-type: none"> Hematuria/proteinuria Electrolyte abnormalities Acute tubular necrosis Acute kidney injury 	<p><i>Multifactorial</i></p> <ul style="list-style-type: none"> Direct viral injury Endothelial dysfunction leading to <ul style="list-style-type: none"> • vasoconstriction • microvascular dysfunction Systemic inflammatory response ("cytokine storm") Immune complexes Hypovolemia
<p><i>Hepatic/Gastrointestinal</i></p> <ul style="list-style-type: none"> Liver function tests abnormalities Gastrointestinal symptoms (diarrhea, abdominal pain, nausea, vomiting) 	<p><i>Multifactorial</i></p> <ul style="list-style-type: none"> Direct viral injury Endothelial dysfunction <ul style="list-style-type: none"> • proinflammatory • procoagulant • proaggregating Microvascular small bowel injury Systemic inflammatory response ("cytokine storm") Hypoxia-associated metabolic abnormalities
<p><i>Neurologic/ocular</i></p> <ul style="list-style-type: none"> Ageusia, anosmia Dizziness, headache, seizures Guillain-Barré syndrome Encephalitis/meningoencephalitis Encephalomyelitis Acute hemorrhagic necrotizing encephalopathy Conjunctivitis and retinal changes 	<p><i>Multifactorial</i></p> <ul style="list-style-type: none"> Direct nervous system invasion for ageusia, anosmia, encephalitis, meningoencephalitis Direct viral injury Endothelial dysfunction <ul style="list-style-type: none"> • proinflammatory • procoagulant Systemic inflammatory response ("cytokine storm") Postinfectious/immune-mediated for Guillain-Barré syndrome, encephalomyelitis, acute hemorrhagic-necrotizing encephalopathy Direct viral injury and inflammation for conjunctivitis

reported. Endothelium represents an interface between blood and body's tissues.²⁴ The broad spectrum of clinical manifestations, affecting almost all organs and systems, is a consequence of the endothelial dysfunction and systemic inflammatory response. As shown in **Tables 1-3**, endothelial dysfunction's different components and systemic inflammatory response, namely "cytokine storm," play a pivotal role in determining most of the clinical manifestations of COVID-19

(left column) and always underlie severe manifestations.^{4,5}

Recent findings suggest that endothelial dysfunction represents a crucial pathologic characteristic in COVID19, being implicated in microvascular and macrovascular complications associated with the infection, including myocardial infarction and stroke.²⁵ Biomarkers of endothelial dysfunction are increased in patients with COVID-19 and are associated with more severe

Table 3
COVID-19 clinical manifestations by system and pathophysiological mechanism

Clinical Manifestations (Refs. ¹⁻⁵)	Pathophysiological Mechanisms (Refs. ¹⁻⁵)
<p><i>Dermatologic</i></p> <ul style="list-style-type: none"> Acrocutaneous lesions Erythematous and maculopapular rash Vesicles Livedoid, necrotic lesions, petechiae 	<p><i>Multifactorial</i></p> <ul style="list-style-type: none"> Endothelial dysfunction with deposition of microthrombi Systemic inflammatory response (“cytokine storm”) Immune response sensitivity Vasculitis
<p><i>Hematologic</i></p> <ul style="list-style-type: none"> Blood cell count abnormalities (lymphopenia, leukocytosis neutrophilia, thrombocytopenia) Increased inflammatory markers Increased coagulation markers 	<p><i>Multifactorial</i></p> <ul style="list-style-type: none"> Direct viral injury and inflammation and endothelial dysfunction proinflammatory for lymphopenia Systemic inflammatory response and/or bacterial infection for leukocytosis Systemic inflammatory response (early phase) for increased inflammatory markers and increased coagulation makers
<p><i>Miscellaneous</i></p> <ul style="list-style-type: none"> Fever Fatigue Myalgias Endocrine (new-onset diabetes, severe illness in diabetic/obese patients, ketoacidosis) High-grade fever Hypotension Multiorgan dysfunction Disseminated intravascular coagulation Long-term COVID-19 syndrome 	<ul style="list-style-type: none"> Cytokine release common to other virus for fever, fatigue, and myalgias Direct viral injury, lactate level increase, low oxygen, and low pH for myalgias Multifactorial for endocrine Endothelial dysfunction leading to systemic inflammatory response (“cytokine storm”) ACE2 viral binding on beta cells Impaired counter-regulation (not specific to COVID-19) Altered immune response (not specific to COVID-19) Systemic inflammatory response for high-grade fever, hypotension, and multiorgan dysfunction Endothelial dysfunction leading to coagulation/fibrinolytic abnormalities, macro- and microthrombosis, bleeding for disseminated intravascular coagulation Multifactorial for long-term COVID Virus-specific pathophysiologic changes Inflammatory damage and immunologic aberrations Sequelae of postcritical illness

forms of the disease and high mortality.²⁶ Endothelial dysfunction may result from a combination of direct viral effects, as suggested by the presence of viral elements within the endothelium in autopsies from patients who died of COVID19, and a consequence of virus-dependent activation of inflammatory response.²⁷ Moreover, endothelial changes are multiorgan, indicating that endothelial dysfunction may be involved in numerous symptoms of SARS-CoV-2-positive patients.²⁸ Injury of endothelial cells is involved in several pathophysiological mechanisms that may promote the

occurrence of micro- and macrovascular involvement in COVID19 infection. Endothelial cells activated by a hyperinflammatory state induced by viral infection may promote localized inflammation, increase reactive oxidative species production, and alter dynamic interplay between the procoagulant and fibrinolytic factors in the vascular system, leading to thrombotic disease not only in the pulmonary circulation but also in peripheral veins and arteries.²⁹ It was proposed that mitochondrial dysfunction and oxidative stress, induced by viral infection, can initiate a feedback

loop, promoting a chronic state of inflammatory cytokine production and endothelial alteration even after the viral particles have been eliminated from the body.³⁰ Agents that limit endothelial dysfunction may mitigate the proinflammatory and prothrombotic state induced by COVID-19 infection; therefore, targeted inhibition of cytokines, major effectors of endothelial activation, represents a more focused approach than generalized antiinflammatory agents. Some clinical trials that use strategies aimed to have inhibit the inflammasome–interleukin-1 β (IL-1 β)–IL-6 pathway already yielded preliminary results; some, but not all, indicate signals of efficacy being a critical aspect in the maintaining of the balance between the potential benefits versus the potential of lowering immunologic defences.²⁴

ADAM17 Abridges COVID19 and Endothelial Dysfunction

ADAM17 (a disintegrin and a metalloproteinase 17) is a type I transmembrane protein that belongs to a superfamily of Zn-dependent metalloproteases. ADAM17 plays a key role in the regulation of the proteolytic release from cellular membranes of some cytokines, chemokines, growth factors, and their receptors, affecting downstream signaling and cellular responses. Increased ADAM17-mediated shedding has been described in a variety of diseases such as ischemia, heart failure, arthritis, atherosclerosis, diabetes, cancer, neurologic, and immune diseases. Tissue inhibitor of metalloproteinase 3 (TIMP3), a key endogenous inhibitor involved in regulation of the activity of matrix metalloproteinases and ADAMs, is the only known physiologic inhibitor of ADAM17. Previous reports have implicated the ADAM17/TIMP3 dyad as a mediator between metabolic stimuli, inflammation, and innate immunity.³¹ The increased activity of ADAM17 has been correlated with increased insulin resistance and hyperglycemia. Furthermore, the upregulation of ADAM17 activity increased insulin receptor resistance in patients with type 2 diabetes.³² Several data support the involvement of an increased activity of ADAM17 in both COVID-19's comorbidities and SARS-CoV-2 infection. In fact, the ADAM17 upregulation leads to the ACE2 ectodomain proteolytic cleavage, facilitating viral entry, and to the cleavage of tumor necrosis factor alpha and IL-6R and other proinflammatory molecules, contributing to the "cytokine storm" and reinforcing the inflammatory process during SARS-CoV-2 infection. This hyperinflammatory state has deleterious effects on the vascular system with resulting endothelial cell dysfunction and not only affects local

endothelial function but can also provoke a prothrombotic and antifibrinolytic imbalance in blood that favors thrombus accumulation.³³ Coagulation abnormalities and disruption of factors released by endothelial cells represent also the common pathophysiological link between SARS-CoV-2 infection and the cardiovascular events, including acute cardiac injury, stroke, heart failure, arrhythmias, and cardiomyopathies. In particular, the molecular interaction of SARS-CoV-2 with the ACE2 receptor located in the endothelial cell surface, either at the pulmonary and systemic level, leads to early impairment of endothelial function, which, in turn, is followed by vascular inflammation and thrombosis of peripheral blood vessels.³⁴

In this context, the worse clinical outcome observed in patients with COVID-19 with diabetes may be in part related to the increased ADAM17 activity and its unbalanced interplay with ACE2. Therefore, strategies aimed to inhibit ADAM17 activity may be explored to develop new effective therapeutic approaches.

SUMMARY

In the last 2 years a great progress had been made to provide mechanisms explaining how Sars-COV-2 affects human health. Data point to endothelium as a major site of action of the virus. The overactivation of the physiologic functions of endothelium such as control of vasomotion, vascular permeability, fibrinolysis and hemostasis, inflammation, and oxidative stress may contribute to the COVID19 disease and provide a framework to develop new therapeutics against Sars-COV-2 in the future.

CLINICS CARE POINTS

- Endothelial dysfunction represents a crucial pathologic characteristic in COVID19, being implicated in microvascular and macrovascular complications associated with the infection, including myocardial infarction and stroke.
- Endothelial dysfunction may result from a combination of direct viral effects, as suggested by the presence of viral elements within the endothelium in autopsies from patients who died of COVID19, and a consequence of virus-dependent activation of inflammatory response.
- Treatment encompasses oxygen (when required); symptomatic, antiinflammatory, antiviral, and anticoagulant drugs (prophylactic or therapeutic, with low-molecular-weight heparin), and monoclonal antibodies.

CONFLICTS OF INTEREST/DISCLOSURES

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