 doi:10.20944/preprints202004.0204.v1

Is COVID-19 an endothelial disease? Clinical and basic evidence

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 doi:10.20944/preprints202004.0204.v1

Abstract

The symptoms most commonly reported by patients affected by coronavirus disease 2019 (COVID-19) include cough, fever, and shortness of breath. However, other major events usually observed in COVID-19 patients (*e.g.* high blood pressure, thrombosis, pulmonary embolism) seem to suggest that the virus is targeting the endothelium, one of the largest organs in the human body. Herein, we report both clinical and preclinical evidence supporting the hypothesis that the endothelium is a key target organ of COVID-19.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 13 April 2020 doi:10.20944/preprints202004.0204.v1

Introduction

Coronavirus disease 2019 (COVID-19) represents a public health crisis of global proportions. Caused by SARS-CoV-2, which stands for *severe acute respiratory syndrome coronavirus 2*, COVID-19 was first announced in December 2019 in Wuhan, the capital of China's Hubei province, and has since spread globally[1]. The symptoms most commonly reported include cough, fever, and shortness of breath. The pathophysiology of the disease explains why respiratory symptoms are so common: indeed, the virus accesses host cells via the protein angiotensin-converting enzyme 2 (ACE2)[2, 3], which is very abundant in the lungs[4]. Nevertheless, ACE2 is also expressed by endothelial cells (ECs)[5, 6], and other major clinical events usually observed in COVID-19 patients (*e.g.* high blood pressure[7], thrombosis[8], pulmonary embolism[9]) seem to suggest that the virus is targeting the endothelium, one of the largest organs in the human body[10].

Pathogenesis of COVID-19

SARS-CoV-2 uses a surface glycoprotein (peplomer) called spike to access host cells and ACE2 has been shown to be a co-receptor for coronavirus entry[11, 12]. Therefore, the density of ACE2 in each tissue may correlate with the severity of the disease in that tissue[13-16]. Other receptors on the surface of human cells have been suggested to mediate the entry of SARS-CoV-2[3], including transmembrane serine protease 2 (TMPRSS2)[17], sialic acid receptors[18, 19], and extracellular matrix metalloproteinase inducer (CD147, also known as basigin)[20].

Intriguingly, all of these 4 receptors are known to be expressed by ECs[21-24] (**Figure 1**). ACE2 remains the most studied of these receptors[16, 25-29]: for instance, its genetic inactivation has been shown to cause severe lung injury in H5N1-challenged mice[30], whereas administration of recombinant human ACE2 ameliorates H5N1 virus-induced lung injury in mice[30]. Importantly, ACE2 is currently at the center of a heated debate among cardiologists[31-34], and there are concerns that medical management of hypertension, including the use of inhibitors of the renin-angiotensin-aldosterone system (RAAS), may contribute to the adverse health outcomes observed[16, 35, 36]; TMPRSS2 has been shown to bind the viral spike glycoprotein[17]; recent structural

assays have suggested that coronaviruses can bind sialic acid receptors[18]; CD147 has been shown to be essential for the entry of cytomegalovirus into ECs[24].

Endothelial dysfunction refers to a systemic condition in which the endothelium loses its physiological properties, including the tendency to promote vasodilation, fibrinolysis, and anti-aggregation; moreover, endothelial dysfunction appears to be a consistent finding in patients with diabetes[37]. Here we will discuss clinical and preclinical findings supporting our hypothesis that COVID-19 impairs endothelial function (**Figure 2**).

Hypertension and COVID-19

Several investigators have called attention to the potential over-representation of hypertension among patients with COVID-19[38, 39]. Moreover, hypertension appears to track closely with advancing age, which is emerging as one of the strongest predictors of COVID-19–related death[8, 40]. Specifically, observational trials and retrospectives studies conducted near Wuhan area have actually shown that hypertension is the most common co-morbidity observed in patients affected by COVID-19, ranging from 15 % to 31.2%[8, 41-44]. The largest study has been conducted by Guan and colleagues between December 11, 2019, and January 29, 2020, providing data on 1099 hospitalized patients and outpatients with laboratory-confirmed COVID-19 infection[41]; in this cohort, 165 of them (~15%) had high blood pressure[41]. The authors also evaluated the severity of disease, and the composite outcome of intensive care unit (ICU) admission, mechanical ventilation and death, concluding that 23.7% of hypertensive patients had disease severity (vs 13.4% of normotensive subjects), and that 35.8% (*vs* 13.7%) reached the composite endpoint of ICU admission, mechanical ventilation and death[41]. The high rate of hypertensive patients in COVID-19 was later confirmed in a prospective analysis on 41 patients admitted to hospital in Wuhan[42] as well as in a large study conducted on 138 hospitalized patients with confirmed COVID-19 infection[43]. Notably, in the latter report, the rate of hypertension was 31.2%, and 58.3% of hypertensive patients with COVID-19 infection were admitted to ICU compared to 21.6% of individuals with normal blood pressure[43]; evidencing the hypertensive state as a common co-

morbidity and cause of ICU admission in COVID-19 patients[43]. Similarly, among 191 COVID-19 patients from Jinyintan Hospital and Wuhan Pulmonary Hospital, 58 (30%) of them had hypertension, and 26 of them (48%) did not survive COVID-19, whereas 32 (23%) were survivors[8]. Finally, the 30% rate of hypertensive patients was further confirmed in an analysis based on the severity of COVID-19 conducted on 140 patients in Wuhan: 58 patients were classified as severe *vs* 82 patients classified as no severe: hypertensive patients represented 37.9% of severe *vs* 24.4% of no severe COVID-19 patients[44]. Overall, these findings confirm a dual aspect of hypertension during COVID-19 pandemic: first, hypertension is the most common co-morbidity observed in COVID-19 patients; second, hypertension is evidenced in patients with worse prognosis and higher rate of death.

These studies also raise numerous questions regarding the association between hypertension and COVID-19. Indeed, it is well known that hypertension is one of most common disease and co-morbidity worldwide, considered a silent killer for worldwide population[45]. We speculate that the higher rate of hypertension and the worse prognosis in patients with COVID-19 infection could be seen as the spy of a cause-effect mechanism more than of a casual pre-existing association between these two different diseases.

Recent reports evidenced higher morbidity and mortality rates of COVID-19 in African-Americans compared to Caucasian subjects in United States[46]. Of note, several studies have shown a higher prevalence of hypertension in blacks than in whites[47], and ACE inhibitors (ACEi) and angiotensin II receptor blockers (ARS) have not been shown to be as effective in black populations compared with white populations[48].

ACE2 and anti-hypertensive drugs: what do we know?

ACEi and ARS represent very effective strategies for the treatment of hypertension[45]. These drugs reduce the effects of renin-angiotensin axis by inhibiting ACE (ACEi) or by blocking the angiotensin receptors (ARS). A rising question for the scientific community and physicians is to understand whether ACEi/ARS could affect the prognosis of hypertensive COVID-19 patients[16, 49, 50].

Unfortunately, there are no data regarding specific anti-hypertensive medications and hypertensive COVID-19 patients with infection.

The role of ACEi/ARS in the control of ACE2 molecular pathways is controversial: indeed, preclinical studies evidenced that the selective blockade of either angiotensin II synthesis or activity in rats induces increases in ACE2 gene expression and activity[51-54]; similarly, treating infarcted rats with ARBs increased plasma concentration of angiotensin 1–7 and ACE2[55]. In mice, ARB treatment augmented ACE2 mRNA and protein levels[56, 57] and prevented the decrease in ACE2 protein levels induced by Angiotensin II[58]. Equally important, mineralocorticoid receptor blockers prevented aldosterone induced reduction in cardiac ACE2 mRNA expression in rat cardiomyocytes[59] and increased ACE2 expression and activity in murine hearts and in monocyte-derived macrophages obtained from 10 patients with heart failure[60].

Nevertheless, there is no clinical evidence that ACEi directly affect molecular pathways linked to ACE2 activity. For instance, urinary ACE2 levels were reported to be higher in patients treated with olmesartan *vs* untreated controls, but this finding was not observed in patients treated with other ARS or enalapril[61]; instead, another study reported no difference in ACE2 activity in patients who were taking ACEi or ARS *vs* untreated patients[49]. Of note, clinically prescribed ACEIs have been shown to not inhibit ACE2, which function as a carboxypeptidase[62]. In particular, ACE2 acts to counterbalance the effect of ACE[63]: indeed, whereas ACE generates angiotensin II from angiotensin I, ACE2 converts angiotensin II into an active heptapeptide (angiotensin 1-7) with vasodilative, anti-oxidant, and anti-inflammatory properties[64-66].

Some media sources have recently called for the discontinuation of ACE inhibitors and angiotensin-receptor blockers (ARBs), both prophylactically and in the context of suspected COVID-19[67]. Given the common use of ACE inhibitors and ARBs worldwide, guidance based on experimental evidence on the use of these drugs in patients with COVID-19 is urgently needed. Notably, there is no evidence regarding the effects of ACEi/ARS on circulating ACE2 expression and/or lung-specific expression of ACE2 during COVID-19 infection. Therefore, we can only speculate that human ACE2 expression can vary, and it could be altered by hypertension and/or by other pathological conditions as during COVID-19 infection. On the other hand, even assuming that

ACEi/ARS could modify ACE2 levels and/or activity in humans, current studies cannot indicate if these effects could favor an enhanced engagement and/or entry of COVID-19 in humans.

The binding of the SARS-CoV-2 spike protein to ACE2 has been suggested to cause the down-regulation of ACE2 from the cell membrane[68]. Consequently, ACE2 down-regulation could lead to a loss of protective effects exerted by ACEi/ARS in humans[69]. Such down-regulation of ACE2 is an attractive research field[54, 70]. Indeed, it could be a valid therapeutic target to ameliorate response and clinical prognosis in hypertensive patients affected by COVID-19. Moreover, some investigators proposed the restoration of ACE2 by administration of recombinant ACE2 to reverse the lung-injury process during viral infections[2]. Actually, these effects are being investigated in ongoing clinical trials (*ClinicalTrials.gov* NCT04287686), alongside the use of losartan as first therapy for COVID-19 in hospitalized (NCT04312009) or not hospitalized patients (NCT04311177). A major role in the pathogenesis of (as well as in the clinical response to) COVID-19 could be also played by ACE2 polymorphisms, which are relatively under-investigated if compared to ACE[71, 72].

Finally, we have to consider the higher rate of cardiac injury and adverse outcomes in hypertensive patients during COVID-19 pandemic[48, 73, 74]. Therefore, ACEi/ARS chronic therapy should not be discontinued in hypertensive patients with COVID-19. Indeed, the loss of their pneumo- and cardio-protective effects could be detrimental[45]. In addition, in absence of adequate follow-up visits, switching from ACEi/ARS to another anti-hypertensive therapy could cause a suboptimal control of blood pressure. Thus, as suggested by several medical associations[67], in absence of definitive clinical studies and without clear evidence, hypertensive patients should avoid discontinuation and/or therapeutic switching during COVID-19 infection.

Diabetes and COVID-19

Diabetes mellitus is a frequent co-morbidity and a cause of worse prognosis in patients with COVID-19 infection[75-77]. Indeed, evaluating pneumonia cases of unknown causes reported in Wuhan and in patients with history of exposure to Huanan seafood market before Jan 1, 2020,

20% had diabetes[42]. Similarly, among 1099 COVID-19 patients analyzed by Guan and colleagues, 7.4% had diabetes: this percentage goes up to 16.2% among patients with severe disease (*vs* 5.7% in patients with non-severe disease)[41]; furthermore, 35.8% of patients experiencing the composite endpoint of ICU admission, mechanical ventilation and death, had diabetes (*vs* 13.7% of patients that did not experience such endpoint)[41]. In summary, diabetes is a frequent co-morbidity, a risk factor, and an independent prognostic factor in COVID-19 patients. A strong evidence of the negative effects of diabetes in COVID-19 patients is confirmed by two meta-analyses[78, 79].

The worse prognosis in patients with diabetes and COVID-19 could be attributable to the fact that the pneumonia evolves towards clinical stages more refractory to medical therapies, oxygen administration and mechanical ventilation, with necessity of ICU care. These data have been investigated in a previous study conducted in patients with SARS[80], in which the relationship between a known history of diabetes and fasting plasma glucose (FPG) levels with death and morbidity rate was assessed, showing that the percentage of patients with diabetes was significantly higher in deceased *vs* survivors (21.5% *vs* 3.9%, $P < 0.01$)[80]. Moreover, diabetics with hypoxemia ($SaO_2 < 93\%$) had higher FPG levels and FPG was independently associated with an increased hazard ratio of mortality (1.1, 95% CI: 1.0-1.1) and hypoxia (1.1, 95% CI: 1.0-1.1) after controlling for age and gender[80]. The authors concluded that diabetes (3.0, 95% CI: 1.4-6.3) and FPG > or = 7.0 mmol/l (3.3, 95% CI: 1.4-7.7) were independent predictors of death[80].

In COVID-19 patients, the incidence of diabetes is two-folds higher in ICU/severe *vs* non-ICU/severe cases[79]. Indeed, the diagnosis of diabetes in a cohort of patients with COVID-19 Infection evidenced a sub-group of patients with a 2.26-fold higher risk to experience adverse disease outcome analyses[78]. Unfortunately, no data are available on anti-diabetic medications and glucose homeostasis in COVID-19 patients. This aspect is really limiting, because the diagnosis of diabetes diagnosis and the altered glucose homeostasis during a condition of severe pneumonia with SARS are reported as main factors of worse prognosis and deaths[80]. Therefore, the investigation of anti-diabetic medications and glucose homeostasis could be harnessed to evaluate patients with higher risk to experience worse prognosis and death by COVID-19. We speculate that

the amelioration of glucose homeostasis in diabetic COVID-19 patients by specific hypoglycemic drugs could result in the amelioration of clinical outcomes with death reduction. However, these data are not reported in trials on COVID-19, and they need to be investigated in further studies.

Thrombosis and COVID-19

Patients with COVID19 often show clotting disorders, with organ dysfunction and coagulopathy, resulting in higher mortality[81]. Important data came from the analysis of coagulation tests including prothrombin time (PT), activated partial thromboplastin time (APTT), antithrombin activity (AT), fibrinogen, fibrin degradation product (FDP), and D-dimer, in samples collected on admission and during the hospital stay of COVID-19 patients[82]. Non-survivors patients had significantly higher D-dimer and FDP levels, and longer PT *vs* survivors on admission[82]. Moreover, significant reduction and lowering of fibrinogen and AT levels were observed in non-survivors during late stages of hospitalization, which is compatible with a clinical diagnosis of disseminated intravascular coagulation (DIC)[82]. Hence, COVID-19 patients develop DIC, especially during the late stages[83]. Specifically, among 191 COVID-19 patients seen at two hospitals in Wuhan, D-dimer levels over 1 μg/L at admission predicted an 18-fold increase in odds of dying before discharge[8]. Of note, when DIC is caused by a systemic infection, it features an acute systemic over-inflammatory response, strictly linked to endothelial dysfunction[84].

A dysregulated immune response, as seen in COVID-19, especially in the late stages of the disease, is known to play a decisive role in endothelial dysfunction and thrombosis[85, 86], and microvascular permeability is crucial in viral infections[87]. Indeed, pulmonary endothelium represent a fundamental barrier between the blood and interstitium and has vital regulatory functions; specifically, ECs represent 1/3 of the cell population of the lung[88], and pulmonary endothelial damage is considered the hallmark of acute respiratory distress syndrome (ARDS)[89]. Animal models of coronavirus-induced severe ARDS have shown that reduced ACE2 activity and loss of ACE2 in the lungs is mirrored by enhanced vascular permeability, and exacerbated pulmonary edema[66]. Acute pulmonary embolism (APE), reported in COVID-19 patients[90, 91], has been shown to be a cause of clinical deterioration in viral pneumonias[92, 93]. Intriguingly, endothelial dysfunction

is known to be a key determinant in hypertension, thrombosis, and DIC[94-98]. A retrospective analysis evaluated 25 patients with COVID-19 pneumonia, who had a median of D-dimer of 6.06 μg/ml and underwent computed tomography pulmonary angiography (CTPA) to detect APE[9]. From this analysis, 10 patients had APE confirmed by CTPA. APE was mainly found in small branches of the pulmonary artery, and in 3 patients there was partial or complete thrombus absorption after anticoagulant therapy[9]. Henceforth, it is important to select COVID-19 patients at higher risk of APE, and practice CTPA for APE diagnosis especially in case of significant increase of D-dimer values. Anticoagulation could be a necessary therapy to control and reduce pro-thrombotic events, as well as to prevent APE[99].

Anticoagulation as a therapy for COVID-19.

As discussed before, COVID-19 infection could cause endothelial dysfunction and a hyper-coagulation state. This condition is aggravated by hypoxia, which augments thrombosis by both increasing blood viscosity and hypoxia-inducible transcription factor-dependent signaling pathway[100]. Consequently, these phenomena could result in APE with occlusion and micro-thrombosis in pulmonary small vessels, as observed in critical COVID-19 patients[101]. Apart from cases of APE, COVID-19 can cause a sepsis-associated DIC, that is defined “sepsis-induced coagulopathy” (SIC)[84]. Thus, there is an increasing interest for the anticoagulant therapy for COVID-19. In a retrospective analysis conducted at Tongji Hospital of Huazhong University of Science and Technology in Wuhan, the authors examined 449 patients affected by severe COVID-19[99]. The diagnosis of severe COVID-19 disease was made by evidence of respiratory rate≥30 breaths/min, arterial oxygen saturation ≤93% at rest and PaO_2/FiO_2 ≤300 mmHg[99]. In these patients, they reviewed and compared the parameters of coagulation tests and clinical characteristics between survivors and non-survivors to evaluate the effects of heparin therapy[99]: 94 patients received low molecular weight heparin (LMWH, 40-60 mg enoxaparin/day) and 5 received unfractioned heparin (UFH, 10000-15000 U/day), without other anticoagulants[99]. Heparin therapy significantly reduced mortality in patients with SIC score ≥4 (40.0% *vs* 64.2%, $p<0.05$), but not in those with SIC score <4 (29.0% *vs* 22.6%, $p>0.05$)[99]. D-dimer, PT, and age were positively, while

platelet count was negatively correlated with 28-day mortality[99]. In addition, stratifying by D-dimer values the study population, the authors reported in heparin nonusers a rise of mortality linked to the rising D-dimer, and 20% reduction of mortality for patients under heparin with D-dimer exceeding 3.0 μg/mL[99]. Therefore, heparin treatment appears to be associated with better prognosis in severe COVID-19 patients with coagulopathy. The full clinical evaluation of patients with COVID-19 infection cannot leave aside from the analysis of laboratory and imaging data. We believe that PT/PTT, fibrinogen, and D-Dimer should be monitored daily and anticoagulation therapy should be recommended for COVID-19 patients when the D-Dimer value is 4 times higher than the normal upper limit, except for patients with anticoagulant contraindications. The confirmed diagnosis of severe COVID-19 disease in patients with hypercoagulation and organ failure could evidence an early stage of sepsis-induced DIC. On the other hand, anticoagulant may not benefit unselected patients. Consequently, further prospective studies are needed to confirm this result in COVID-19 patients, also testing other antiaggregants and anticoagulants (at different doses), including novel direct oral anticoagulants (NOAC or DOAC).

Other therapeutic approaches

Recently, chloroquine and hydroxychloroquine have been suggested as a potential therapy for COVID-19[102, 103], although the exact molecular mechanisms remain unknown; if our hypothesis on the key role of ECs in COVID-19 disease is confirmed, these drugs may exert their beneficial effects via an amelioration of endothelial dysfunction. Indeed, consistent with our view, both these antimalaric agents have been shown to improve endothelial function[104, 105] and to alter the glycosylation profiles of ACE2 by increasing the pH of intracellular organelles, including lysosomes and Golgi[106]. Strikingly, similar findings have been reported for colchicine[107], azithromycin[108], and tocilizumab[109], recently proposed as treatment for COVID-19[102, 110].

Funding: The Santulli's lab is supported in part by the NIH (R01-HL146691, R01-DK033823, R01-DK123259, P30-DK020541, and R00-DK107895 to G.S.) and by the American Heart Association (AHA-20POST35211151 to J.G.).

Conflict of interests: none.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 13 April 2020 doi:10.20944/preprints202004.0204.v1

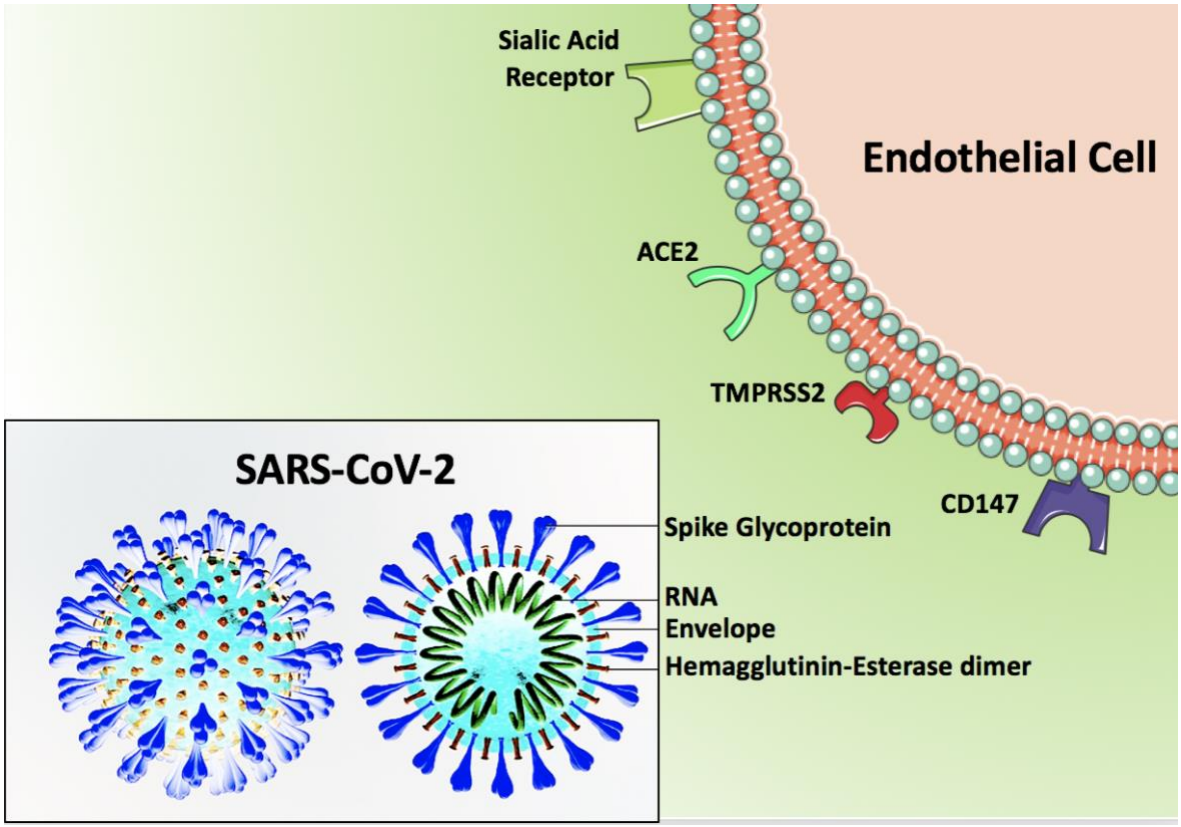

Figure 1.

Pathogenesis of COVID-19.

The SARS-CoV-2 coronavirus accesses host cells via the binding of its spike glycoprotein to angiotensin-converting enzyme 2 (ACE2), sialic acid receptor, transmembrane serine protease 2 (TMPRSS2), and extracellular matrix metalloproteinase inducer (CD147).

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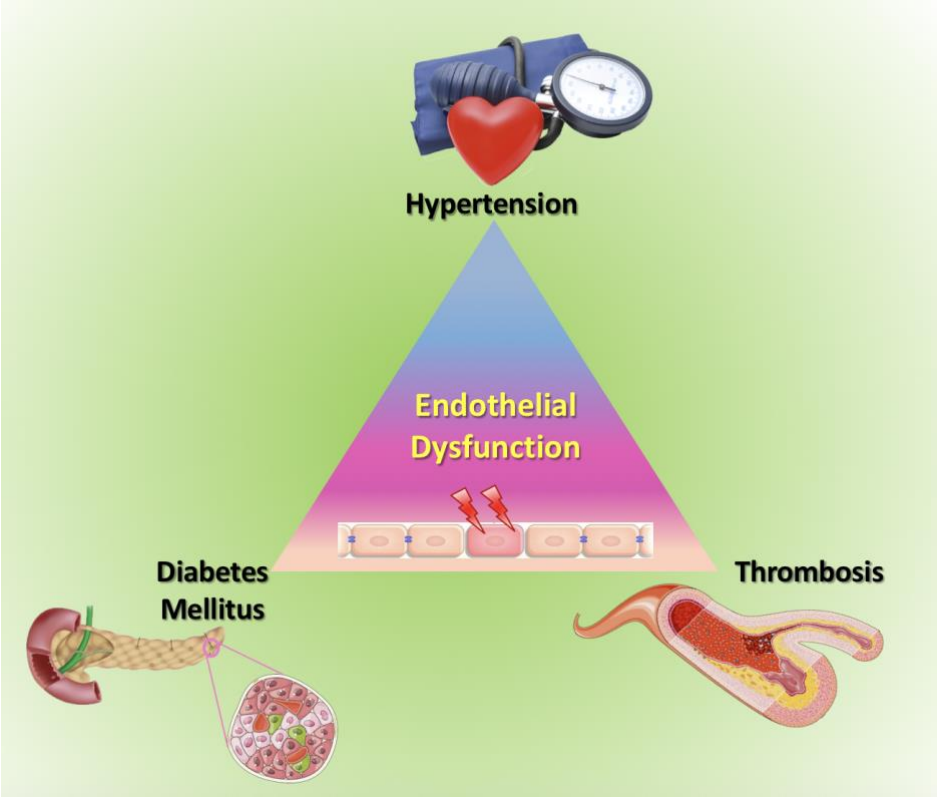

Figure 2.

Endothelial dysfunction is a major determinant of COVID-19.

Endothelial dysfunction is a common feature of hypertension, diabetes, and thrombosis, critical clinical findings in COVID-19 patients.

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