Abstract

The role of the renin–angiotensin system (RAS) and its pharmacological modulators in the susceptibility and outcomes of SARS CoV-2 pandemic (COVID-19) has been much discussed recently. Angiotensin-converting enzyme type 2 (ACE2) has attracted much attention and debate in relevance to COVID-19. It not only acts as the receptor to which the SARS CoV-2 virus binds to be introduced into cells but also balances the effects of angiotensin II offering anti-inflammatory and antifibrotic protective actions to different organs. This mini-review aims to shed some light on the possible involvement of ACE2 and RAS alternate pathways in the comorbidities and clinical findings observed in COVID-19 patients.

Keywords: Angiotensin-converting enzyme 2, COVID-19, renin–angiotensin system

Introduction

Angiotensin-converting enzyme 2 (ACE2) is a key player in COVID-19, as it is the coronavirus CoV-2 receptor that facilitates viral invasion of cells, but on the other hand, it exhibits a protective role in COVID-19 pathogenesis.

There are two kinds of ACE2 in the human body: a circulating ACE2 in the blood and a transmembrane receptor. ACE2 receptor N-terminus is found in many organs including the heart, kidneys, gastrointestinal tract (GIT), and lungs, particularly in type 2 pneumocytes.\(^1\) The expression of ACE2 in the lung is age and gender related. Men express more ACE2 than women, while its expression level is negatively correlated with age.\(^2\) Higher expression of ACE2 in men probably explains why male gender is considered as a risk factor for higher severity and poorer outcome in COVID-19 patients. On the contrary, elderly patients showed higher mortality,\(^3\) which suggest that other factors besides ACE2 levels might affect the disease course.

It has been shown that ACE2 is the receptor for both coronavirus CoV-2 and SARS-CoV, due to their homology and similar structure, with 10–20-fold higher binding affinity to coronavirus CoV-2, which might explain its higher contagiousness.\(^4\) It is also well known that ACE2 is the component of renin–angiotensin system (RAS) that regulates the levels of angiotensin II (Ang II); consequently, ACE2 downregulation with coronavirus CoV-2 invasion would shift the RAS axis toward excessive Ang II production. Ang II blood levels have been found to be significantly increased in COVID-19 patients, showing a linear correlation with viral load and lung injury.\(^5\)

This mini-review aims to:
• Enhance the understanding of the renin angiotensin system involvement in COVID-19 pathophysiology
• Elucidate issues that necessitate further investigation in that important topic related to COVID-19.

Lung Pathogenesis

In response to pulmonary Covid-19 viral invasion, the ACE2 gets decreased resulting in higher Ang II level. Binding with AT1 receptors, Ang II enhances vascular permeability, pulmonary edema and activation of the pro inflammatory cascade with enrollment of more macrophages. Macrophages release

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cytokines that pursue recruitment of more neutrophils and CD4 T-cells resulting in severe inflammation, which, together with vascular leakage, are characteristic of acute lung injury/severe acute respiratory distress associated with COVID-19. Moreover, Ang II induces JNK phosphorylation and apoptosis through the AT1 receptor in alveolar epithelial cells.

Kuba et al. showed increased lung Ang II levels in SARS-CoV spike protein-treated mice which correlated to worsening of acute respiratory distress syndrome symptoms. The severity of symptoms was partially reversed by blocking the AT1 receptors. Due to the homology between the spike protein of SARS-CoV and that of SARS-CoV-2, COVID-19 infection is also expected to increase Ang II in the lung. Evaluating the components of the RAS in lung autopsies is required to elucidate the mechanisms involved in lung injury in COVID-19 cases.

It should be taken into consideration that Ang II acting through AT2 receptors in the pulmonary epithelium exhibits antifibrotic and anti-inflammatory effects, but it was observed that in patients with chronic obstructive pulmonary disease, there was a 5–6 fold increase in the ratio of AT1 to AT2 receptors in the lungs. Chen et al. found that Ang II is profibrotic and induces collagen accumulation and lung fibrosis. Consequently, the possibility of alteration in the balance of these receptors in the lungs of COVID-19 patients needs to be evaluated.

One of the earliest autopsy studies on deceased COVID-19 cases revealed the presence of fibrin thrombi within the lung capillaries, and another study in Italy revealed fibrin thrombi of pulmonary vessels in 33/38 patients, with high levels of D-dimer in blood. Both studies suggest thrombotic microangiopathy as an important mechanism that might contribute to death in COVID-19 cases.

Ang 1–7 is a degradation product of Ang II under the effect of ACE2 and has been proved to have protective effects against thrombosis. As levels of Ang 1–7 are probably downregulated in COVID-19 cases, a randomized, controlled Phase II/Phase III trial has been recently designed in Erasmus University Hospital, Brussels, Belgium, to test the clinical impact of Ang 1–7 infusion in COVID-19 patients with respiratory failure requiring mechanical ventilation.

Severe cases of COVID-19 probably suffer an imbalance between alternative pathways of RAS activation which underlies the pathophysiology of acute lung injury/severe acute respiratory distress. Further assessment of all RAS components is recommended for better understanding of its contribution to the progress and outcomes of the disease and for setting appropriate therapeutic measurements.

RENIN–ANGIOTENSIN SYSTEM CARDIAC PATHOGENESIS

Cardiomyocytes, cardiac fibroblasts, and endothelial and smooth muscle cells show a wide expression of ACE2. Furthermore, degradation products produced by ACE2 proved cardioprotective through antihypertrophic, antifibrotic, and antithrombotic effects. Cardiac troponin I and N-terminal pro–B-type natriuretic peptide were found to be elevated in COVID-19 patients besides to arrhythmias, and this raised the notion of viral myocarditis in SARS-CoV 2, although fulminant myocarditis in response to cytokine storm was also suggested. This was challenged in the published data on the first cardiac autopsy of COVID-19 cases, which revealed individual cell myocyte necrosis and few lymphocytes adjacent to degenerating myocytes.

Nicin et al. compared the expression of ACE and ACE2 in the different cardiac cell types between normal heart and patients with heart failure and aortic stenosis. ACE2 in cardiomyocytes of patients with heart disease was significantly elevated compared with healthy hearts. Moreover, patients treated with ACE inhibitors showed higher ACE2 expression with more than 4-fold increase in ACE1/ACE2 ratio. The currently increasing debate on the impact of ACE inhibitors and AT1 receptor blockers on COVID-19 is crucial since the use of these drugs increases ACE2 expression which enhances susceptibility to viral invasion but might ameliorate the ongoing pulmonary and cardiac pathology.

PANCREATIC PATHOGENESIS

As the human endocrine pancreas expresses ACE2, the coronavirus might enter islets and cause acute β-cell dysfunction. This was postulated in the study of Yang et al. on 39 SARS-CoV patients. The authors reported that 20 of 39 patients, who were not diabetic, nor received corticosteroids prior to the illness, developed diabetes during the SARS-CoV infection and two of them remained diabetic after 3 years.

In the literature, only one study monitored glycemic status in COVID-19 patients and followed blood glucose levels of 1000 patients in US hospitals between March 1 and April 6, 2020. Mortality was found to be increased 7-fold in COVID-19 patients who were not diabetic prior to infection but developed uncontrollable hyperglycemia in hospital. This observation raises attention to possibility of pancreatic beta-cell damage in COVID-19 patients.

From a different perspective, diabetic patients are prone to infections, and this may increase the morbidities and mortality of COVID-19 in diabetic patients. Brufsky 2020 suggested that uncontrolled hyperglycemia upregulates glycosylated ACE2 which favors viral invasion.

GASTROINTESTINAL TRACT PATHOGENESIS

Different segments of the gastrointestinal system including esophagus, stomach, small intestine, and colon and especially the enterocytes are known to express ACE2, and stool samples of many COVID-19 cases tested positive for the SARS-CoV2 virus RNA. A study of 95 COVID-19 patients showed that 58 cases suffered GIT symptoms, of which 11 (11.6%) occurred
on admission, excluding the possibility that these symptoms were due to the side effects of pharmacological measures given to patients. Endoscopy was carried out in some patients and revealed esophageal bleeding and ulcers, and SARS-CoV-2 RNA was detected in the esophagus, stomach, duodenum, and rectum specimens from severe cases. Diarrhea, nausea, and vomiting were the most common GIT presentations, pointing to the fact that the GIT might be a target for SARS-CoV-2 virus.[26,27]

**Neuronal Pathogenesis**

Many COVID-19 patients experienced neurological manifestations that ranged from headache and dizziness to more severe Guillain–Barré syndrome, encephalitis, stroke in otherwise healthy young cases, and even necrotizing hemorrhagic encephalopathy.[28,29] Vascular endothelial cells express ACE2, and upon binding of SARS-CoV-2 virus in infected patients, breaching of the blood–brain barrier may result in leading to viral invasion of the brain.[30] Another proposed explanation for the neurological symptoms in COVID-19 patients is the presence of ACE2 in neurons and glial cells allowing direct infection with the virus.[31] Li et al. 2020[32] proposed that SARS-CoV-2 virus invasion of the brainstem might underlie impairment of the function of the respiratory centers leading to respiratory failure in COVID-19 patients, although many authors refer the neurological manifestations to the altered activity of inflammatory markers and cytokine storm in COVID-19 patients.[33]

**Skin Pathogenesis**

ACE2 expression was evident in the basal cell layer of the epidermis and extended to the basal cell layer of hair follicle.[34] Interestingly, several types of skin rash were observed in COVID-19 patients.[35] A study in Spain demonstrated that 47% of COVID-19 patients developed maculopapular rash.[36] Although skin manifestations could be explained by the immune reaction and cytokine storm, viral presence in the lesions should be investigated and verified.

**Renal Pathogenesis**

The availability of ACE1 within the renal cortex was found to be higher than in cardiac muscle,[37] and level of ACE2 was dramatically decreased upon inducing kidney injury in mice.[38] In addition, in patients with diabetic nephropathy, the level of ACE1 was increased while the level of ACE2 was reduced.[39] This points to the important role of RAS in regulation of kidney function.

Renal function abnormalities have been reported in COVID-19 patients. There was an increased incidence of acute kidney injury as a major complication of COVID-19 infection and was considered as a measure of severity and a risk factor for mortality.[40] Severe kidney injury was reported in 7% of 41 patients with COVID-19 infection.[41] Moreover, urine samples were positive for COVID-19 in infected patients. Cheng et al. 2020, assessed the association of kidney affection with mortality rate in seven hundred COVID-19 patients. The authors reported that infected patients who presented with hematuria, proteinuria and / or elevated levels of blood urea and creatinine, had higher mortality rate than COVID-19 patients with no kidney affection.[40] The effect of COVID-19 infection and the implication of ACE levels in chronic kidney disease should be further investigated.

**Conclusion**

ACE2 is directly linked to the SARS CoV-2 viral invasion of multiple organs.

Imbalance between the alternate pathways of RAS may explain many pathophysiological mechanisms that underlie morbidity associating COVID-19.

Components of the RAS are a potential area for investigation in COVID-19. In addition, potential pharmacological strategies involving the RAS for treatment of COVID-19 have been discussed recently, although it must be cautioned that, at present, these are only of theoretical benefit.

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**Conflicts of interest**

There are no conflicts of interest.

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