Review Article

# Gastrointestinal and kidney manifestations in SARS-CoV and SARS-CoV-2 infections: role of angiotensin-converting enzyme 2

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## ABSTRACT

The emergence of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in 2020, which has a substantial structural similarity to severe acute respiratory syndrome coronavirus (SARS-CoV) that caused the outbreak in 2003, is currently a threat to global health. Lung involvement is the principal clinical feature in infected patients but extra-pulmonary clinical presentations are also common. The reasons for the extensive involvement of other organs are not yet clear. Angiotensin-converting enzyme 2 (ACE2), the key peptide of renin–angiotensin system (RAS), has recently identified as a major receptor for the both SARS-CoV and SARS-CoV-2 that might be a main target of coronavirus infection. ACE2 is mainly expressed in the pulmonary pneumocytes, the small intestine enterocytes as well as the proximal tubule epithelial cells of the kidneys. In addition to the respiratory tract infection symptoms, the noticeable prevalence of gastrointestinal symptoms as well as kidney impairment in hospitalized infected patients highlights other routes of infection/transmission. In present review, we discussed the role of RAS with emphasis on ACE2 in the pathogenesis of SARS-CoV and SARS-CoV-2, particularly in gastrointestinal and kidney manifestations of the diseases.

## Introduction

The recent outbreak and rapid spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel human Coronavirus disease 2019 (COVID-19) infection in Wuhan of China has caused considerable global health consternation. The SARS-CoV-2 demonstrated an 82% nucleotide identity with severe acute respiratory syndrome coronavirus (SARS-CoV), which caused the global outbreak in 2003 (Silva-Antonialli et al., 2004). Both SARS-CoV and SARS-CoV-2 are single-stranded enveloped RNA viruses that belong to the β-genus of the coronavirus family (Lu et al., 2020). SARS-CoV-2 shares many clinical characteristics with SARS-CoV such as severe

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atypical pneumonia, gastrointestinal (GI) symptoms and occasional kidney failure (Khot and Nadkar, 2020). The main clinical features of SARS-CoV-2 are as follows: fever (the most common presenting symptom; 83-98%), cough (59-82%) accompanying with expectoration (27-28%), as well as myalgia and fatigue (11-69%). Upper respiratory symptoms (0-5%) is less common in SARS-CoV-2 infection compare to SARS –CoV (Chen et al., 2020; Huang et al., 2020; Wang et al., 2020a). Main complications such as acute respiratory distress syndrome (31-55%), acute cardiac injury (7-12%) and acute kidney injury (3-7%) have also been found during hospitalization which bring great inconvenience for the patients management (Chen et al., 2020; Huang et al., 2020; Wang et al., 2020a).

While COVID-19 has higher transmissibility through the respiratory tract, clinical and laboratory data supporting an additional role of GI tract in disease transmission. It has revealed that both above coronaviruses employ angiotensin-converting enzyme 2 (ACE2) as the host cell receptor for infectious entry into target cells (Letko et al., 2020). ACE2 receptor is mainly expressed in human lower airway as well as the GI tract and kidney. It means that coronaviruses may enter different tissues through their special receptor and causing various organ damages.

According to the clinical case data in the SARS outbreak, 16–73% of patients had diarrhea during the first week of illness (WHO, 2003). SARS-CoV RNA was detected in stools from the fifth day of illness onwards, which progressively increased and peaked at day 11 of the illness and a small proportion of stool specimens of patients with SARS were positive for viral RNA even after 30 days of illness (Chan et al., 2004). Other organ damage resulted from coronavirus has also been reported; for example, a detailed retrospective study showed that while acute renal injury is infrequent in SARS but may carry a high mortality risk (91.7%) (Chan et al., 2004).

The ACE2 expression profile in different organs, tissues and cell types may indicate the potential infection routes of both SARS-CoV and SARS-CoV-2 and benefit the investigation of diagnosis and treatment strategies. This review highlights the function of renin angiotensin system (RAS), with emphasis on the role of ACE2 receptor in the pathogenesis of SARS-CoV and SARS-CoV-2 infections, particularly in gastrointestinal

and kidney damages.

*The renin–angiotensin system*

The RAS is a complex enzymatic-hormonal network which participates in the regulation of the blood pressure, fluid homeostasis and electrolyte balance, as well as function of several organs. The octapeptide angiotensin II (AngII) is an important biological product of this system (Aros and Remuzzi, 2002). Moreover, other peptides including angiotensin III, angiotensin IV and angiotensin 1-7 are active in this system (Reudelhuber, 2005). In the classical pathway, renin is released from renal juxtaglomerular cells, which generates Ang I from angiotensinogen in the plasma. Ang I is cleaved to Ang II by ACE in the lungs. Angiotensin II exerts its effects by binding to two G-protein-coupled receptors, Ang II type 1 and 2 receptors (AT1R and AT2R) (Zaman et al., 2002). It has recently been shown that the ACE homologue ACE2 converts angiotensin I to angiotensin1-9 which is subsequently converted to angiotensin1-7 by ACE (Boehm and Nabel, 2002; Donoghue et al., 2000; Zaman et al., 2002). As a part of the presser arm of the RAS, Ang II promotes sodium retention and decrease in glomerular filtration rate, vasoconstriction, hypertension, as well as renal injury through the AT1R activation (Silva-Antonialli et al., 2004). However, the AT2R is a part of the depressor arm of the RAS and acts as a physiological antagonist of the AT1R. Besides that, ACE2 and angiotensin 1-7 are other components of the depressant arm of the RAS (Lakzaei et al., 2019 ; Santos et al., 2005). Angiotensin 1-7 exerts its vasodilator and antiproliferative effects via the Mas receptor (Boehm and Nabel, 2002; Donoghue et al., 2000; Santos et al., 2005).

In addition to the circulating (systemic) RAS, there are local RAS that are expressed in various organs such as kidney, lung and GI tract. Numerous studies have confirmed the presence of all components of this system in the kidney tissue (Cat and Touyz, 2011). Ang II can damage renal tissue through both hemodynamic and non-hemodynamic pathways (Gharaei et al., 2019 ; Safari et al., 2015; Safari et al., 2019). Its hemodynamic effects are exerted through an increase in the vascular tone and effect on hydrostatic pressure, glomerular filtration and filtration fraction (Yoshioka et al., 1987). While it induces its non-hemodynamic effects through the release of reactive oxygen species, cytokines,

profibrotic growth factor and aldosterone (Ruiz-Ortega et al., 2001). Therefore, Ang II may play an important role in the kidney damage through different mechanisms.

Endothelial-bound ACE2 and its homolog ACE, are belong to the M2 family of metalloproteases. Both of these enzymes have an active extracellular domain that facilitates the metabolism of circulating peptides, and zinc is essential for their catalytic activity (Donoghue et al., 2000). ACE generates angiotensin II, the most important effector peptide of the RAS, and ACE2 is responsible for the breakdown of angiotensin II. Up to now, three main functions have been identified for ACE2. 1- It acts as a negative regulator of the renin-angiotensin system and neutralizes the functions of the ACE; 2- With targeting angiotensin II, it plays a protective role in several organs such as cardiovascular system; 3- ACE2 has a key role in amino acid absorption in the kidney and gut (Kuba et al., 2010).

*Interaction SARS-CoV and SARS-CoV2 with ACE2*

SARS-CoV and SARS-CoV2 have a highly homolog structure. Binding of both coronaviruses to the ACE2 for entering into host cells is mediated via the viral surface spike glycoprotein (S-protein). A defined receptor-binding domain of S-protein specifically identifies its host receptor ACE2. For the virus infectivity, the inactive form of precursor S protein should be cleavage by the host cell proteases. Studies have shown that after binding the S protein to the ACE2, SARS-CoV2 activates the trans-membrane protease serine 2 (TMPRSS2) and allows the virus to fuse with the host cell membrane. Other studies revealed that TMPRSS2 activates SARS-CoV for the host cell entry and confirmed the expression of TMPRSS2 in type II pneumocytes (Glowacka et al., 2011; Matsuyama et al., 2010; Shulla et al., 2011). It has also been suggested that the activity of endosomal cathepsins, specially cathepsin L is essential for the entrance of infectious SARS-CoV into cell lines. However, several studies showed that the TMPRSS2 along with or instead of cathepsins may be used for SARS-CoV activation in main target cells. Other studies revealed co-expression of ACE2 and TMPRSS2 in other organs such as GI tract and suggested that TMPRSS2 is likely promote the extra-respiratory spread of SARS-CoV. Therefore, the SARS-CoV may employ TMPRSS2 to ensure its activation in the target cells.

Compared to SARS-CoV, the binding affinity of ACE2 to SARS-CoV2 receptor-binding domain is much higher, explaining why SARS-CoV2 seems to be more readily transmissible between humans. Therefore, it can be concluded that ACE2 and TMPRSS2 expressions are important determinants of the coronavirus entry into the host cell. The binding of SARS-CoV2 to ACE2 down-regulates the ACE2 expression and thus leads to increases in Ang II. It has suggested that the therapies that increase ACE2 may have a protective role against the coronavirus induced lung injury.

*RAS involvement in GI pathophysiology*

There is now a significant body of literature demonstrating the RAS involvement in GI physiology and pathophysiology. The RAS is implicated in the gastrointestinal fluid and electrolyte homeostasis, glucose and amino acid transportation, control of motility and blood flow. The involvement of RAS in some pathological processes within the GI tract has been documented, such as esophageal motility disorders (Fändriks, 2011), gastric ulcerations (Carl-Mcgrath et al., 2009; Hallersund et al., 2011; Lüdtke et al., 1989; Seno et al., 1997), inflammatory bowel disease (Matsuda et al., 2001; Silverstein et al., 1981; Sommer et al., 1986; Takeuchi et al., 1992), irritable bowel syndrome and malignancy (ARB Trialists Collaboration., 2011; George et al., 2010; Pasternak et al., 2011; Sipahi et al., 2010). Therefore, the GI RAS can be considered as a possible target for novel investigative and therapeutic approaches in GI disorders.

*GI signs and symptoms of Coronavirus infection*

While SARS-CoV-2 infection of respiratory epithelial cells is spread mainly through the respiratory tracts, the virus has been detected in the COVID-19 patients' stool specimen in the recent investigation, indicating the possibility of the virus extra-respiratory infection and an alternative route for virus transmission (Holshue et al., 2020). Several tissues and organs can be infected by the coronavirus and the alimentary tract is a well-established target of SARS-CoV (Ding et al., 2004). The GI symptoms of these patients are included: nausea and vomiting (14–22.2%), diarrhea (7–73%) and abdominal pain (3.5–12.6%). Although GI symptoms such as nausea, vomiting (1-3.6%) and diarrhea (2%) in COVID-19 patients were less common in formerly series (Chen et al., 2020; Huang et al., 2020), but later studies

reported anorexia (39.9%), diarrhea (10%), nausea and vomiting in about 8% and nonspecific abdominal pains (8%) more frequently in infected patients (Wang et al., 2020a).

These atypical GI symptoms were manifested in patients even before subsequent severe respiratory symptoms. The Coronavirus-like particles has been shown in the intestinal mucosal epithelial cells and mild focal inflammation was distinguished in the GI tract. In spite of viral adhesion and colonization, no villous atrophy has been reported. Another study demonstrated the presence of virus in the dilated endoplasmic reticulum of the intestinal epithelial cells. The viral load variability and the strength of the immune responses could influence the variances in clinical symptoms and GI impairment among different patients. The presence of the SARS-CoV in GI epithelial cells has been imagined by electron microscopy; however, no evidence of gut mucosa, submucosa inflammation and villous dampening in patients with SARS-CoV associated diarrhea was documented (Leung et al., 2003).

Diarrhea has been reported as the most common GI symptoms, occurring in 74% of all SARS-CoV cases. Many treated cases complained of anorexia and generalized abdominal pain even 10-20 days after negative PCR of respiratory tract specimens and negative blood tests (Miri et al., 2020). Furthermore, viral RNA has been detected in 97% of fecal specimen of SARS patients, as well as in the stool samples of COVID-19 patients even 17 days after viral clearance in the respiratory tract (Xiao et al., 2020), implied the possibility of feco-oral transmission. The nasopharyngeal viral load has been considerably higher in patients with diarrhea and in those who died compared to that in the other SARS patients; however, diarrhea has been shown to predict poor outcome (Cheng et al., 2004).

The binding affinity of coronavirus for its host receptor, ACE2, is known as one of the determining factors in infectivity and it has suggested that SARS-CoV-2 uses ACE2 more efficiently than SARS-CoV (Wan et al., 2020). Several studies have shown ACE2 association with GI function. Highly expression of ACE2 mRNA in gastrointestinal system is necessary for maintaining amino acid homeostasis, expression of peptides with antimicrobial activity and the microbial ecology in the intestine (Hashimoto et al., 2012; Vuille-Dit-Bille et al., 2015).

*RAS involvement in the Coronaviruses pathogenesis*
*Oral cavity*

ACE2 expression on the mucosa of oral cavity and lymphocytes within oral mucosa has demonstrated in recent studies (Xu et al., 2020). The expression of ACE2 has been higher in the epithelial cells of tongue than buccal or gingival tissues (Xu et al., 2020). A number of studies have shown that coronavirus infections hardly presented oral symptoms; however, the expression of ACE2 in the oral tissues has indicated the possible oral infection route of SARS-CoV-2.

Although the ACE2-positive lymphocytes proportion is fairly small (Xu et al., 2020), whether the Coronaviruses would attack the lymphocytes and its possible effect on the severity of illness needs more *in vitro* and *in vivo* studies. SARS-CoV-2 has been detected in the saliva of patients with rectal swabs tested positive to SARS-CoV-2 (Guan et al., 2020). Thus, oral cavity could be regarded as potentially high risk for SARS-CoV and SARS-CoV-2 infectious susceptibility and fecal–oral transmission might be the one of the routes of coronaviruses transmission.

*Esophagus*

Several studies confirm the expression of the renin-angiotensin system in the human esophagus. The main effector peptide of RAS, AngII, as well as angiotensinogen and renin have been detected in the esophageal musculature (Björkman, 2012). In addition to the substrate AngII, the presence of the additional angiotensins, Ang1-7, AngIII and AngIV, have also been confirmed. Furthermore, immunoreactive AT1R and AT2R have been identified in the superficial stratified epithelium and the two muscle layers (circular and longitudinal). Likewise, both Ang II receptors besides ACE have been recognized in the lamina propria of the microvascular walls. Another study has shown that renin, ACE and two AngII receptors are present at the gastroesophageal junction (Resende and Mill, 2002).

Esophagus RAS components modulate electrical resistance, epithelial ion transport and muscle contractions, which in turn could influence the mucosal barrier properties (Casselbrant et al., 2009). It has suggested that the local esophageal RAS might be involved in the epithelial barrier damage in gastroesophageal reflux disease (Björkman, 2012).

Following virus entrance in the cytoplasm, the RNA and proteins specialized to virus are synthesized to assembly new versions, which can be released to GI tract. Although SARS-CoV-2 RNA has been identified in esophageal mucous tissue, seldom ACE2 protein staining in esophageal mucosa has been reported (Xiao et al., 2020). Intracellular viral protein staining has shown that ACE2 protein is abundantly expressed in the glandular epithelial cells of stomach, duodenum and rectum, allowing the virus entry into the cells (Fändriks, 2011). Hence, rarely ACE2 protein staining is probably due to squamous epithelial cells composition of esophageal epithelium (Xiao et al., 2020). The effects of Coronaviruses on the esophagus have not yet been reported. It is confirmed the importance of ACE2 protein expression for Coronavirus infection.

### Stomach

RAS components are present in the antrum and body of the stomach of healthy adults. Renin and angiotensinogen: both renin and angiotensinogen have been seen in lamina propria mesenchymal cells and vascular endothelium (Garg et al., 2012). ACE and ACE2: ACE has detected in vascular endothelium, fundic chief cells and mucin cells of the antrum (Carl-Mcgrath et al., 2009). Another study demonstrated ACE2 protein expression in the gastric glandular epithelial cells (Xiao et al., 2020). Angiotensinogen receptors: both AT1R and AT2R have been detected in the stomach epithelium, lamina propria mesenchymal cells and vascular endothelial cells. AT1R was also distinguished in the base of antral mucosal glands.

Longitudinal and circular gastric muscles have been confirmed to respond to Ang II, suggesting the presence of proper Ang II receptors on gastric myocytes (Lüdtke et al., 1989). Limited data are available regarding functional or pathogenic roles of the RAS in the stomach. Higher expression of AT1R in helicobacter pylori (H. pylori) positive patients compare to H. pylori negative ones may suggest a role for the RAS in gastric inflammation (Hallersund et al., 2011). However, to the best of the authors' knowledge, the pathological effects of Coronaviruses on the stomach have not been reported until present.

### Small and large intestines

The highest human tissue concentrations of ACE and ACE2 mRNA have been reported in the duodenum, terminal ileum and colon (Harmer et al., 2002; Tipnis et al., 2000). The components required for the local action of RAS are all presented in the small intestine. ACE and ACE2: A human study has shown abundantly expression of ACE in the mesenteric microvascular endothelial cells and on the epithelial brush border (Bruneval et al., 1986). Highly expression of ACE2 mRNA and protein has reported in the brush border of intestinal epithelial, muscularis mucosa and propria, Paneth like cells, goblet cells, enteroendocrine cells, vascular smooth muscle cells and microvascular endothelial cells (Hamming et al., 2004).

Angiotensin receptors: AT1R is mainly expressed in the epithelial brush border, both intestinal muscle layers (circular and longitudinal), the myenteric plexus as well as small vessels in the muscularis propria (Ewert et al., 2006; Shorning et al., 2012; Spak et al., 2008), but the AT2R expression is restricted to the myenteric plexus (Ewert et al., 2006; Spak et al., 2008). Renin and angiotensin peptides: renin mRNA has been detected in the small intestine (Shorning et al., 2012) and Ang II has been found in the epithelial cells of crypt and crypt-villus junction (Seo et al., 1991). Another study has shown expression of ACE2 protein in large amounts in the brush border of enterocytes of entire parts of the human small intestine.

RAS is involved in a diversity of intestinal processes including 1- absorption of sodium and water: the jejunum and ileum sodium and water absorption has shown been to be modulated by Ang II (in an interaction with enteric sympathetic nervous system) (Levens, 1986; Levens et al., 1981); 2- bicarbonate secretion: Ang II through its receptors, AT1R and AT2R, stimulated bicarbonate secretion in the duodenum (Johansson et al., 2001); 3- peptides digestion and absorption: this process is thought to involve two brush border peptidases, ACE and ACE2, so ACE and ACE2 work as digestion-related enzymes in human enterocytes (Bai, 1994; Erickson et al., 1992).

*In situ* hybridization examinations have detected SARS-CoV in the intestinal surface enterocytes (Leung et al., 2003). Furthermore, active viral replication has been revealed in the enterocytes and detection of SARS-CoV RNA in patients' stool samples has been reported in another study (Ding et al., 2004). On the other hand, ACE2 as the common receptor for both SARS-CoV and

SARS-CoV-2, is highly expressed in human enterocytes (Feng et al., 2020). Due to the function of ACE2 in intestinal fluid and electrolyte absorption, a modulating effect on fluid shifts across the brush border and, after that, the effect on stool consistency and frequency has been suggested for it. Watery diarrhea has been reported in some patients with Coronavirus infection, so ACE2 may play a role in intestinal active secretion in Coronavirus infected patients (Hamming et al., 2004).

SARS-CoV and SARS-CoV-2 have common ancestors and target the same host cells in the small intestine. Enterocytes function as the conserved cell reservoirs for Coronaviruses has been suggested in some studies. Throughout the evolution, the binding receptor and binding modes of Coronaviruses are persistently changed; however, the possible target cell in the small intestine is more likely constant. Given the highly expression of ACE2 in the enterocytes, small intestine can be considered as an underestimated site of SARS-CoV-2 infection (Feng et al., 2020). High expression of ACE2 in the intestine reduces intestinal inflammation through the expression of antimicrobial peptides and maintaining the gut microbial ecology (Hashimoto et al., 2012; Vuille-Dit-Bille et al., 2015).

Because of the closely relation to the small intestine, microbiota may also change the Coronaviruses receptors expression. Qi et al. has reported that throughout the infection of intestine with *Salmonella enterica*, enterocytes number with high Coronaviruses receptors expression were increased, and suggested that it may raise the accessibility of coronaviruses to enterocytes (Feng et al., 2020). Probiotics are commonly used for the diarrhea treatment in COVID-19 patients. However, because of the complicated composition of the enteric microbiome and the limited public data related to probiotics, the utility of probiotics for SARS-CoV and SARS-CoV-2 infected patients may still need further investigation.

RAS comportments are distributed and expressed in the colon as follows. ACE and ACE2: low expression of ACE has been detected in parts of the colon surface epithelium, in mesenteric microvascular walls, lamina propria and mesenchymal cells in the submucosal compartment (Hirasawa et al., 2002). Another study reported highly expression of ACE2 by the colonocytes (Wang et al., 2020b) and Hamming et al. (2004) has found that ACE2 expression is mostly restricted to the colonic mesenteric microvascular endothelium. A study has shown co-expression of TMPRSS2 and ACE2 in the colon and suggested that the extra respiratory spread of SARS-CoV might be promoted by TMPRSS2. Renin: renin is mostly distributed in the epithelium, mesenchymal cells of the colon lamina properia, muscularis mucosa as well as microvascular walls (Hirasawa et al., 2002).

Angiotensin receptors: AT1R has been detected on surface epithelium, in the bases of crypts, the macrophages of lamina propria, myofibroblasts and mucosal vessel walls. Low expression of AT2R has been shown in surface epithelial cells, crypts and mesenchymal cells (Hirasawa et al., 2002). *In vivo* studies revealed that Ang II increases reabsorption of sodium and water through NaCl coupled transport (De Los Rios et al., 1980). Likewise, contraction response of colonic muscle layers to Ang II has suggested a role in normal bowel movements (Macri, 1965). In spite of a relatively normal microscopic and endoscopic appearance, the presence of Coronavirus in the small intestine and colon has been demonstrated by electronic microscopy, viral culture and reverse-transcription polymerase chain reaction (Leung et al., 2003). Another study has shown lymphocytes and plasma cells infiltration without obvious impairment of GI mucosa (Xiao et al., 2020). Minimal disruption of enterocytes by the SARS-CoV infection has been reported, so diarrhea accompanying with this viral infection is more likely related to the proteins or toxins produced during viral replication (Leung et al., 2003).

There is evidence that colonocytes are mostly expressed ACE2 which positively associated with viral entrance (Wang et al., 2020b). Increasing studies have demonstrated that ACE2 expression prevents intestinal inflammation (Hashimoto et al., 2012; Vuille-Dit-Bille et al., 2015; Wang et al., 2020b). Furthermore, human gut studies have suggested that some genes are positively associated with ACE2 expression including the genes involved in viral infection, type I and type III innate immunity, cytotoxicity induced by natural killer and T cells as well as energy metabolism. By contrast, some of them are negatively associated with that such as the genes regulating viral transcription, protein translation, humoral immunity, phagocytosis and activation of complement (Wang et al., 2020b). Thus, a dual mediating role for ACE2 in susceptibility and

immunity to Coronavirus infection has been suggested (Figure 1)Hubei Province, China, in December 2019 and spread rapidly to other provinces and other countries. Angiotensin-converting enzyme 2 (ACE2).

*Renal distribution of ACE and ACE2*

Although angiotensinogen is mostly synthetized in the liver, there is evidence that this protein is also expressed in the kidneys. In this context, both Ang mRNA and protein have been detected in the proximal tubules. Some studies have suggested that the Ang protein is not present in the kidney tissue in physiological conditions, but its expression increases under pathological conditions such as hypertension (Kobori et al., 2007; Matsusaka et al., 2012). Renin is expressed in juxtaglomerular cells of adult renal tissue, which are located in the median layer of the afferent ant efferent arterioles (Prieto-Carrasquero et al., 2004). Moreover, renin activity and its mRNA can be detected in the proximal convoluted and straight tubules (Chen et al., 1994). Some recent studies have reported renin localization in the distal tubule (Prieto-Carrasquero et al., 2004); however, it has not been seen in the medullary collecting ducts (Chen et al., 1994).

The distribution of ACE and ACE2 in different areas of kidney tissue are not the same. An *in vivo* study has shown simultaneous expression of ACE and ACE2 in the brush board of apical membrane of proximal tubular cells. While ACE exclusively present in glomerular endothelial cells, ACE2 is expressed in podocytes and minimal expression of that has also detected in glomerular mesangial cells (Ye et al., 2006). The expression of ACE and ACE2 in the brush border of human proximal tubular cells has been reported, but glomerulus has a lower density of both above enzymes (Mounier et al., 1987; Reich et al., 2008). Immunoelectron microscopic studies have confirmed the presence of ACE in the proximal tubules and glomerular endothelial cells. Furthermore, ACE has been detected in the vascular endothelium of the kidneys (Mounier et al., 1987).

*Renal damage in Coronavirus infection*

Clinical studies on the patients with SARS-CoV infection have shown that some of them have experienced renal dysfunction and failure, and need dialysis. The time between infection onset and renal failure has lasted approximately 20 days. The specific symptoms of infected patients were: increased creatinine

levels in 6.7% of patients with a median age of 53.5 years, decreased bicarbonate levels, oliguria in 50% of patients, proteinuria in 84.6%, hyponatremia (sodium <135 mmol/l) in 77.7% and decreased hemoglobin and neutrophils in 77.7% of patients. Pathological findings from renal autopsies have defined some degree of hypertensive nephrosclerosis and tubular atrioventricular necrosis. However, immunofluorescence studies did not confirm the presence of virus particles in the patients' renal tissue. The findings indicate the impairment of renal function and acute tubular necrosis (Chan et al., 2004). Another study has shown an elevated creatinine and also rhabdomyolysis in SARS-CoV patients, which was thought to be likely the cause of kidney damage. However, the follow-up of these patients showed that creatine levels had risen before creatine kinase rose. So they suggested that renal failure could not be due to rhabdomyolysis (Wu et al., 2004). Further studies have revealed that the SARS-CoV increases the levels of cytokines, such as interleukin (IL)-6, IL-8 and the antibodies, while it reduces lymphocyte count (Hsueh et al., 2004). Augmented levels of these interleukins may be involved in renal failure and together with amplified lymphokines may lead to adhesion inflammatory cells to the vascular endothelium and consequently, damage to other organs. Furthermore, It has reported that endothelial vascular dilatation mechanisms are also involved in renal injury (Annuk et al., 2001). Wu et al. (2004) has reported that plasma levels of cytokines may affect mortality and acute renal failure. Together, these findings suggest that renal impairment in SARS-CoV infection is related to the renal immunopathological damage. In fact, an increased host response causes more damage than an uncontrolled virus replication in the body.

Numerous studies have shown that ACE2 is expressed in different parts of the kidney tissue, including the proximal tubule brush border and less commonly in the podocytes. Whereas, it was not detected in glomerular endothelium and mesangial cells. Earlier studies in 2003 reported that only 6 percent of patients with SARS-CoV were developed acute renal failure and of those, 92 percent were died. In this regard, Lai et al. investigated the presence of virus particles in the kidney tissue after patient death. The results of their study showed that no virus particles were found in their renal tissue. They suggested that kidney involvement in these patients was
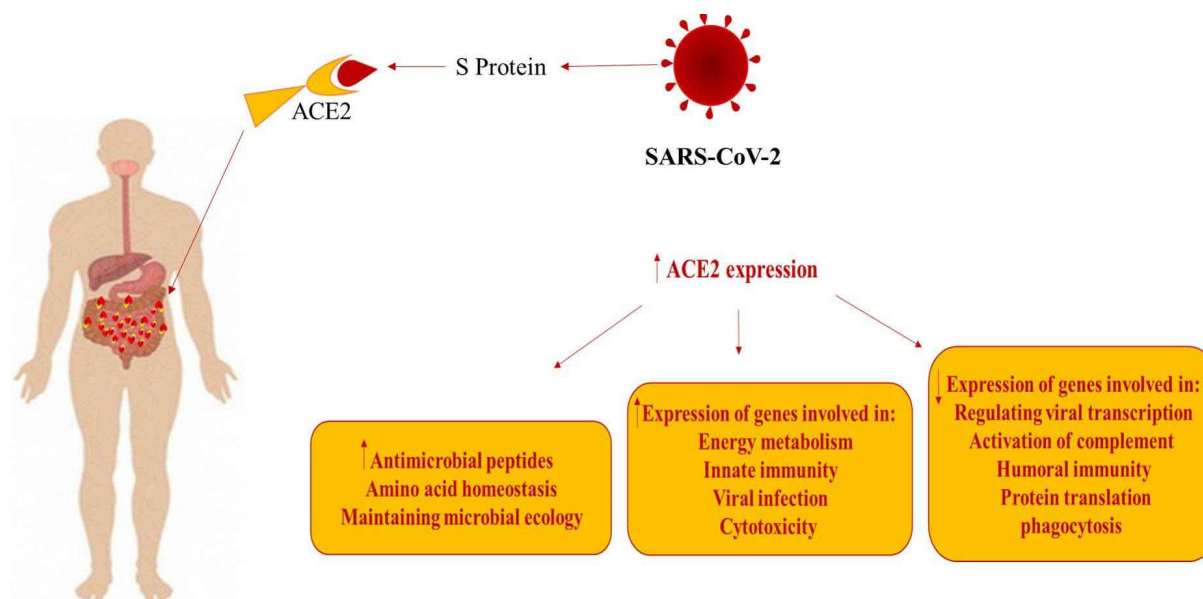
**FIGURE 1.** Dual proposed role for ACE2 in human gut susceptibility/ immunity to SARS-CoV-2 infection. Genes are positively associated with ACE2 expression including: the genes involved in viral infection, type I and type III innate immunity, cytotoxicity induced by natural killer cells and T cells and energy metabolism. By contrast, some of them are negatively associated with that such as: the genes regulating viral transcription, protein translation, humoral immunity, phagocytosis and activation of complement. Thus, a dual mediating role for ACE2 in susceptibility and immunity to coronavirus infection has been suggested. ACE2: Angiotensin-converting enzyme 2; S protein: Spike glycoprotein.

related to the other organs (Chan et al., 2004). Acute renal failure in SARS-CoV patients may lead to a pathological condition, such as cytokine release syndrome (Tisoncik et al., 2012) which eventually causes kidney damage. In fact, lung infection induces immune responses that lead to the release of large amounts of cytokines those results in renal damage. Interferon-gamma cytokine release has been shown to cause damage to other tissues in SARS-CoV patients (Huang et al., 2005). This mechanism is similar to that proposed for kidney damage in cancer patients receiving immune- checkpoint inhibitors, as well as kidney transplant patients receiving thymoglobulin (Moicean et al., 2009).

Although the most well-known effect of COVID-19 is respiratory infection but as previously mentioned, the virus enters the bloodstream after the lung infections and accumulates in some organs like the kidneys and it then induces renal damage. In this regard, studies have confirmed the presence of SARS-CoV-2 in the plasma of 15% of infected patients and about 6.7% of patients with severe infections have developed to acute renal failure. The exact mechanism of kidney damage is not yet being elucidated (Huang et al., 2020), but as explained before, SARS-CoV-2 uses the ACE2 receptor to enter the cell and behaves in a similar way to SARS-CoV. According to human RNA-seq studies, the expression of the ACE2 is 100 times greater in the

kidneys than in the lung and kidneys are one of the main target tissues for the new Coronavirus. Despite of the indirect effect of the SARS-CoV on the kidneys, the kidney effects of SARS-CoV-2 is completely different (Figure 2). Diao et al. confirmed the presence of the viral nucleocapsid protein in kidney tissue after patients died. They suggested that SARS-CoV-2 directly attacks the kidney tissue and could spread in the body (Silva-Antonialli et al., 2004). In fact, the structural differences between these two viruses can be due to the increased SARS-CoV-2 affinity for ACE2, which increases the susceptibility of the kidney to the viral infection (Wan et al., 2020). Another study confirmed hematuria and proteinuria in 40% of COVID-19 patients and increased levels of blood urea nitrogen and creatinine in 19 and 27% of patients, respectively. In this regard, computerized tomography scan of the patient's kidneys also exhibited decreased renal density, suggestive of inflammation and edema (Cheng et al., 2020; Silva-Antonialli et al., 2004).

Various studies have been conducted on renal susceptibility to SARS-CoV-2 infection. The results indicated that the expression levels of ACE2 and TMPRSS in kidney tissue cells are different. ACE2 expression is high in the podocytes and proximal tubules (proximal convoluted tubule and the proximal straight tubule). But the TMPRSS gene is widely distributed in
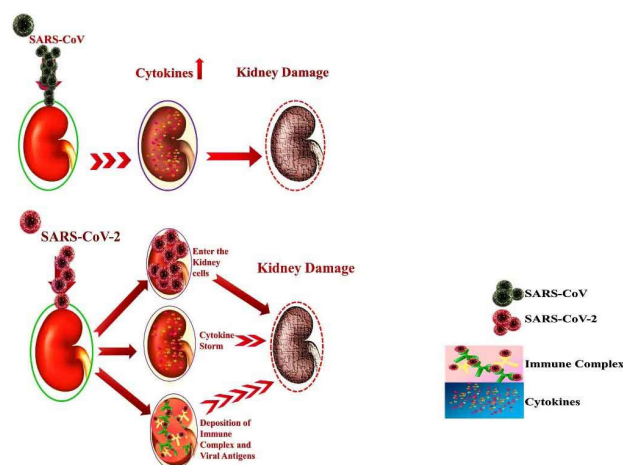
**FIGURE 2.** The possible mechanisms of kidney injury in coronavirus infections (SARS-CoV and SARS-CoV-2). SARS-CoV, only indirectly affects kidney tissue by activating the immune system and increasing cytokines. While, SARS-CoV-2 directly affects kidney tissue by entering the kidney tissue and indirectly by activating the immune system and increasing cytokines and causing damage to it. Dashed lines represent indirect pathways and solid line represent direct pathways.

epithelial cells, especially the collecting duct and distal tubules. The co-localization analyzes of the ACE2 and TMPRSS genes show the high expression of these two genes in the proximal tubules, all epithelial cells and podocytes. (Pan et al., 2020).

Recently, another report on the occurrence of acute kidney injury in people with COVID-19 has been published. It has reported that 83.3-23% of patients in the ICU progress to kidney failure (Huang et al., 2020). Co-expression ACE2 and TMPRSS play important roles in urine formation, reabsorption and urinary excretion. The high expression of these two genes in podocytes predisposes them to COVID-19 damage and proteinuria (Jefferson et al., 2011). But another critical factor is the role of cytokines induced by inflammatory responses in kidney damage. According to the studies carried out, plasma levels of cytokines such as IL-2, IL-7, IL-10, granulocyte colony-stimulating factor, interferon γ–inducible protein of 10 kD, monocyte chemotactic protein 1, macrophage inflammatory protein 1-alpha and tumor necrosis factor alpha are higher in severe infected cases than in mild ones (Huang et al., 2020). So, it can be suggested that the immune system is not only able to kill the virus, but also causes extensive damage to the body's cells. A new study has reported the presence of RNA virus in the urine samples of people with SARS, which may suggest a direct role for Coronavirus in kidney damage (Guan et al., 2020). Thus, the synergistic effect of cytokine and inflammatory responses, and cytotoxic effects of the SARS-CoV2 would lead to acute kidney injury.

Recently, Guan et al. (2020) has shown increased creatinine and urea levels, oliguria, proteinuria, and hematuria in COVID-19 patients. A direct relationship between disease severity and increased creatinine level has been reported. Increased creatinine was concomitant with an increase in leukocytes and decline of lymphocytes and platelets. It has reported that 5.1% of patients with COVID-19 have acute renal failure. The prevalence of acute renal failure was higher in those with elevated blood creatinine levels than the other patients and about 16.4% of patients died on average within 6 days.

Studies on diabetic patients with COVID-19 have shown an increase in ACE2 expression in these patients. On the other hand, treatment with inhibitors of ACE2 and AT2R blockers facilitated infection with SARS-CoV2. This study also reported increased lethal risk of these drugs for consumers infected with SARS-CoV-2. Thus, infection with SARS-CoV-2 may be facilitated by increasing the expression of ACE2 (Wan et al., 2020). Therefore, it can be assumed that in diabetic and hypertensive patients treated with ACE2-stimulating drugs, the risk of developing severe and lethal COVID-19 may increase. Given these results, it can be suggested that SARS-CoV-2 patients have a higher chance of AKF than those with SARS-CoV.

## Conclusion

ACE2 has identified as a non-specific protease and key receptor for both SARS-CoV and SARS-CoV-2, contributing to the GI symptoms and possible renal failure in infected patients. Because of the abundant

expression of ACE2 in the enterocytes as well as renal tubule cells, small intestine and the kidneys can be considered as underestimated sites of viruses' infection. It has shown that highly expression of ACE2 is positively associated with viral entrance to the cell. However, some gastrointestinal studies have suggested a dual role for ACE2 in mediating susceptibility and/or immunity to the virus infection. In terms of renal impairment, the following possible pathways have been suggested for kidney damage in SARS-CoV-2 infection: A) virus enters the cells through ACE2 involving pathway and damages them; B) deposition of immune complexes with virus antigens or virus-specific mechanisms, especially T-lymphocytes and antibodies and C) SARS-CoV-2 induces the production of cytokines and mediators that indirectly affect the kidney and cause renal damage. Whereas, just the last way has been suggested for kidney damage caused by SARS-CoV infection. In sum, in addition to severe acute lung failure, involvement of other organs such as gut and kidney in infected patients appears to be predictive factors for more severe disease outcomes and eventual death. So, local RAS-modulating agents/molecules, specially ACE2, may serve as novel therapeutic agents to treat severe acute lung failure, as well as poor outcomes due to other organ involvement in SARS-CoV and SARS-CoV-2 infections.

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## Conflict of interest

The authors had no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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