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COVID-19 and ACE2 Receptor in Different Tissues: From Pathophysiologic Function To Therapeutic Responses

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ABSTRACT

SARS-CoV-2, the virus responsible for COVID-19, is characterized by its high transmission rate, leading to a global pandemic. Millions of people have lost their lives due to the infection caused by this virus. The ability of the virus to spread rapidly and infect large numbers of people has highlighted the need to understand its mechanisms of infection. Angiotensin-converting enzyme 2 (ACE2) is an essential receptor for SARS-CoV-2 cell entry. SARS-CoV-2 exhibits a high affinity to this receptor and shows high infectivity, leading to an explosive increase in patients infected with COVID-19. ACE2 is the carboxypeptidase homolog of ACE, which produces angiotensin II, the main active peptide of the renin-angiotensin system. From a pathophysiological perspective, this system regulates vital processes across different organs. Additionally, ACE2 enzyme activity could play a protective role against acute respiratory distress syndrome (ARDS) caused by viral pneumonia. Upon infection, SARS-CoV-2 downregulates the expression of ACE2, which is possibly related to the pathogenesis of ARDS. Since this receptor is present in various other tissues such as the heart, kidney, gastrointestinal tract, reproductive system, and sensory organs, it may contribute to pathological symptoms in these organs. Thus, ACE2 is not only a receptor for SARS-CoV-2 but may also play a crucial role in various aspects of the pathogenesis of COVID-19 and potential post-COVID-19 syndromes. Administering ACE2 could competitively bind to SARS-CoV, thereby reducing viral spike protein from attaching to transmembrane ACE2 and consequently reducing viral cell entry into cells and COVID-19 symptoms. In this review, we first examine the role of ACE2 in the pathophysiology of SARS-CoV-2 across different tissues and propose treatment strategies for COVID-19 that involve ACE2.

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1. Context

SARS-CoV-2, responsible for the COVID-19 infection, is considered an epidemic level with a high spread rate, resulting in the loss of millions of lives. The mortality of SARS-CoV-2 infection has significantly increased in individuals with underlying health conditiond including cancer, aging, and cardiovascular diseases (CVDs). Human genetic factors might possibly facilitate the spreade of SARS-CoV-2 (3). Data collected from diverse populations all over the world have indicated that male gender, aging, high body mass index, diabetes mellitus, CVDs, chronic lung diseases, and impaired renal and liver function are key orisk factors of this disease. Patients infected with SARS-CoV-2 typically exhibit symptoms such as fever, cough, dyspnea, fatigue, and muscle cramps. Additionally, SARS-CoV-2 infection might manifest other symptoms including diarrhea, weight loss, nausea and vomiting, headache, dizziness, and chest pain (4, 5).

2. Evidence Acquisition

SARS-CoV-2 infection can lead to respiratory infections, including pneumonia with an estimated mortality rate of 1-2.5%. COVID-19, caused by SARS-CoV-2, is the major public health challenge worldwide. Investigations using chest computed tomography(CT) frequently reveal bilateral ground glass opacities in most infected patients ,indicating SARS-CoV-2-associated pneumonia. Currently, it has been demonstrated that SARS-CoV uses angiotensin-converting enzyme 2 (ACE2) to enter to human cells (6). This virus attaches to the receptor of the ACE2 enzyme, which plays a crucial role in regulating blood pressure and hemodynamics by lowering blood pressure. Its main product, angiotensin (1–7) (Ang (1–7)), binds to the MAS1 proto-oncogeneG protein-coupled receptor (MASR), promoting vasodilation and countering the effects of Ang II. This creates a counterbalancing regulatory pathway to the ACE/Ang II/angiotensin I receptor (AT1R) axis within the renin-angiotensin-aldosterone system (RAAS). ACE2 reduces Ang II levels while increasing Ang (1–7), which helps maintain fluid volume and electrolyte balance. RAAS blockers such as ACE inhibitors (ACEI) and angiotensin receptor blockers (ARBs) are used to manage conditions like systemic hypertension by enhancing the conversion of Ang I and Ang II into Ang (1–9) and Ang (1–7) through ACE2 (7). Distribution and expression of ACE2 in different tissues might be essential for the target organs of SARS-CoV-2 infection. In this study, we will analyze the impact of ACE2 receptor expression across various organs, explore pathways that may induce or exacerbate disease, and discuss the potential use of this receptor as a therapeutic target for COVID-19.

2.1. Coronavirus and its pathogenicity

Coronaviruses have the largest genomes among RNA viruses, containing single-stranded RNA ranging from 27 to32Kbp.The RNAis polyadenylated at the 3’ end and is associated with a nucleocapsid thickness of 9-11 nm. The virus's outer layer features 20 nm petal-shaped spikes resembling a solar crown. Coronaviruses belong to the Nidovirales order, which includes Arteriviridae, Roniviridae , and Coronaviridae. Coronaviridae is divided into alpha, beta, and gamma coronaviruses. Alpha coronaviruses cause gastrointestinal disorders in humans (Table 1) and animals, beta coronaviruses (e.g., SARS-CoV, MERS) cause respiratory illnesses, while gamma coronaviruses infect birds. Coronaviruses are spherical in shape, with a radius typically ranging from 80 to120nm , and contain essential proteins,including S, M, N, and E. The S protein, resembling a petal, facilitates virus binding and entry into host cells via ACE2 receptors and other factors like transmembrane serine protease 2 (TMPRSS2). After binding, the S protein undergoes conformational changes ,leading to membrane fusion and viral entry into the host cell (8, 9).

SARS-CoV-2 primarily infects upper respiratory cells, spreading to alveoli and causing acute lung injury and acute respiratory distress syndrome (ARDS). The virus induces apoptosis through oxidative stress and DNA damage. Poly (ADP-ribose)-polymerase 1, involved in DNA repair, is activated by DNA cleavage, however, is counteracted by the virus's Poly (ADP-ribosyl) glycohydrolase activity, leading to energy depletion and cell death. This oxidative stress and DNA damage contribute significantly to severe lung damage (10, 11). The immune response to SARS-CoV-2 involves antigen presentation, T cell activation, cytokine production, and a cytokine stormthat can lead to inflammation and potential organ failure. Elevated levels of pro-inflammatory cytokines like interleukin 1-β (IL1-β), IL10, and Tumor necrosis factor alpha, are observed, which further exacerbate lung damage and decreased lung capacity (11).

2.2. Physiologic Function of ACE2 Receptor

The human ACE2 gene is positioned on chromosome X (Xp22) and comprises 18 exons. As a conventional zinc

Table 1. Features regarding the strain of human coronaviruses

Species		GeneBank Number	Receptor
Alpha COVID-19	Human coronavirus 229E	AF304460	Aminopeptidase N
	Human coronavirus NL63	AY567487	Angiotensin converting enzyme 2
	Human coronavirus OC43	AY903460	N-acetyl-9-Oacetylneuraminic acid
Beta COVID-19	Human coronavirus HKU1	AY597011	*O*-Acetylated Sialic Acid
	SARS-CoV	AY278741	Angiotensin converting enzyme
	SARS-CoV-2	MT295464	Angiotensin converting enzyme 2

metallopeptidase, it contains 805 residues and is a type I integral membranous glycoprotein with a catalytic domain. Despite its systemic impacts on blood pressure regulation, ACE2 exerts local regulating impacts on the pathologic alterations of various organs, including the lungs, kidneys, and heart. The renin-angiotensin system (RAS) maintains the homeostasis of blood pressure , as well as salt and liquid balance within the body. RAS homeostasis is crucial for both physiologic and pathologic regulation in diverse organs, including the heart, kidneys, and lungs (12). Various studies have described the role of ACE2 in pulmonary diseases, heart failure, kidney diseases, and cancer. Ang II activates various cellular functions and molecular signaling pathways associated with tissue injury, inflammation, and fibrosis. These include calcium mobilization, free radical generation, activation of protein kinases and nuclear transcription factors, recruitment of inflammatory cells, adhesion of monocytes and neutrophils to endothelial and mesangial cells, up-regulation of adhesion molecules, and stimulation of cytokine and chemokine expression, synthesis, and release (13).

Within the RAS, secreted renin produced by juxtaglomerular cellsconverts liver angiotensinogen into angiotensin I (AngI). AngI is an inactive peptide that is converted into AngII by angiotensin-converting enzyme (ACE). AngII is the most potent product of the RAS system which constricts vessels through AT1R. This process consequently stimulates aldosterone production, increases cardiac contraction, promotes oxidative stress, and enhances thrombotic and atherogenic conditions. ARBs are antagonists used to treat of hypertension and cardiovascular disorders. While ACE converts AngI into AngII, ACE2 catalyzes the conversion of AngII into Ang 1-7 by removing a C-terminal phenylalanine amino acid. ACE2 hydrolyzes AngII by its highly potent catalytic efficacy. In contrast to AngII, Ang (1-7) exerts anti-inflammatory and antioxidant features,

offers cardioprotection, possesses antiarrhythmic effects ,and releases vasodilator agents ,including proteinoids and nitric oxide. Indeed, the kallikrein-kinin system (KKS) acts as a regular inhibitor for RAS, primarily functioning to reduce systemic blood pressure and decrease in the production of reactive oxygen species, exerting cardioprotective effects against impairment of heart and kidney damage. The balance between RAS and KKS affects salt sensitivity, blood pressure, sodium excretion, and the volume of circulation by a reduction in reabsorption of sodium through controlling the epithelial sodium channels through bradykinin. Therefore, ACE2 downregulation leads to the enhancement of bradykinin concentration, which is capable of activating bradykinin receptor 2 for vasoconstriction ,as observed during COVID-19 infection. In addition to the membranous form of the ACE2 receptor, a soluble circulatory form is also available at low plasma concentrations , lacking membranous anchors. It has been suggested that soluble form of ACE2 could inhibit the attachment of SARS-CoV-2 to the membranous ACE2 (Figure 1).

Thus, the solution forms of ACE2 may serve as a potential therapeutic strategy for COVID-19 treatment (14-16).

2.3. ACE2 Receptor in the Lung And Facilitation of Infection Dissemination

ACE2 is principally located in the type II pneumocytes of the lungs, though it can alsobe observed in type I pneumocytes and epithelial cells of the respiratory system. Investigations have demonstrated the role of the RAS and ACE2 enzyme in the pathogenesis of acute respiratory distress syndrome. The lowered concentration of ACE2 has been identified in animal models of ARDS, and treatment with external ACE2 has been associated with reduced symptoms of ARDS. ARDS is the most severe form of respiratory infection. Severe forms of respiratory infection, sepsis, aspiration, and trauma could lead to widespread alveolar damage. Pathologic manifestations of

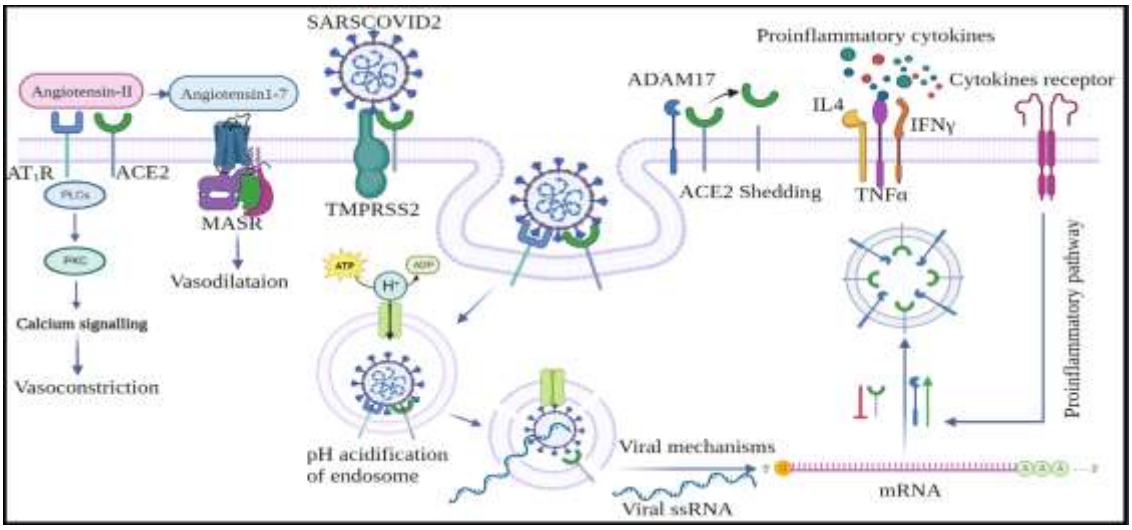

Figure 1. The role of angiotensin-converting enzyme 2 (ACE-2) during SARS-CoV-2 infection. It explains how angiotensin II can bind to either angiotensin I receptor (AT1R) or be processed by ACE2 to generate angiotensin 1-7, which has a vasodilatory effect. During SARS-CoV-2 infection, the viral spike protein binds to ACE2, leading to endocytosis and release of viral RNA into the cytosol. This process involves downregulation of endogenous ACE2 and upregulation of a disintegrin and metalloprotease 17 (ADAM-17), along with activation of proinflammatory pathways by cytokines like tumor necrosis factor-alpha (TNFα), interferon-gamma (IFNγ), and interleukin 4 (IL-4). This figure was adapted from Groß et al. 2020 (2). MAS1 proto-oncogene, G protein-coupled receptor (MASR), transmembrane serine protease 2 (TMPRSS2), phospholipase C (PLC), and protein kinase C (PKC).

ARDS include enhanced capillary permeability, evidenced by the presence of macrophages, neutrophils, and protein-enriched solutions within the alveolar cavity, as well as the formation of hyaline membrane. Inactivation of the ACE2 receptor by SARS-COV-2 leads to the dysregulation of the RAS system.

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Consequently, ACE2 downregulation results in an enhancement of the AngII/Ang (1-7) ratio and an increase in the AngII level, consequently leading to the development of oxidative stress and inflammation.

This process possibly promotes lung injury and tissue fibrosis induced by enhanced vasopermeability (17). In an animal model of acute lung injury induced by acid aspiration, the AngII level was significantly increased in the mouth, lung, and plasma, while ACE inactivation led to the reduced AngII level. Injection of recombinant human ACE2 into the ACE2 knock-out mice and control group, in which both were exposed to acid inhalation, improved lung function and decreased the severity of acute lung injury. Investigations performed on the ACE2 protein level in lung tissues of smokers have demonstrated overexpression of this protein , possibility indicating a higher risk of coronavirus infection. Kuba et al. showed that since ACE2 is an important receptor for the coronavirus, the spike protein bound to ACE2 reduces the ACE2 expression. This reduction in ACE2 further exacerbates acute respiratory failure. Additionally, AngII enhances the expression of profibrotic cytokines, contributing to the development of pulmonary fibrosis and

severe inflammation due to enhanced vascular permeability (18, 19).

2.4. Cardiac ACE2 receptor and development of hypertension

Although ACE2 is expressed in heart and endothelial cells, pericytes have the highest levels of ACE2 expression among cardiac cells. AngII induces inflammation, fibrosis, sodium and water retention, and sympathetic tone via AT1R level. On the other hand, Angiotensin (1-7) inhibits these impacts by attaching to the MASR. Attachment of Angiotensin (1-7) to the MASR results in the arachidonic acid synthesis and nitric oxide synthase activation. ACE2 plays an important role in pulmonary and systemic hypertension, myocardial infarction, heart failure, and cardiovascular complications of diabetes mellitus. ACE2 and Ang 1-7 have a wide spectrum of antioxidant and anti-inflammatory features, which oppose the Ang II functions at vasculatures. Cardiovascular diseases and SARS-CoV-2 share common symptoms such as dyspnea and fatigue , complicating the differential diagnoses. Indeed, significant hypoxemia has been identified as the final pathophysiologic cause of death in both heart failure and SARS-CoV-2 infection (20).

Autopsy studies of 20 patients infected with SARS-CoV have recognized the genome of SARS-CoV in the cardiac tissue of 7 cases ,which was correlated with inflammation, myocardial fibrosis, and downregulation of myocardial ACE2. The importance of SARS-COV-2 infection in the cardiovascular system is reflected by the occurrence of acute myocardial attacks, arrhythmia, septic shock, cardiac arrest, viral myocarditis, and heart failure, as indicated by elevated NT-proBNP and systolic dysfunction discovered by magnetic resonance imaging (21). The cytokine storm induced by SARS-CoV-2 triggers abnormal immune responses and inflammatory plaque rupture, potentially leading to coronary artery thrombosis or spontaneous dissection of coronary arteries, observed in acute coronary syndrome (ACS). Hypoxemia further contributes to the development of ACS, reduced myocardial contraction, increased heart rate, and myocardial infarction. Microvascular injury from vascular thrombosis, intravascular coagulation, disseminated vasospasm, or dysregulated immune response is accelerated after viral infection, leading to the development of left ventricular dysfunction and cardiac failure. Indeed, SARS-COV-2 inhibits the protective pathway in the heart by ACE2 and angiotensin 1-7, which has anti-fibrotic, anti-proliferative, anti-apoptotic and vasodilatory effects (22). Agents capable of regulating RAS have been suggested for the treatment of SARS-COV-2, and the reduction of cardiac complications of infection.

2.5. Renal ACE2 receptor and its role in SARS-CoV-2 infection

ACE2 has a high expression level in the kidneys. RAS is a hormonal system regulating various aspects of renal hemodynamics under both physiologic and pathologic conditions. In this system, ACE2 destroys AngII by proteolysis and forms Ang 1-7. In kidneys, Ang 1-7 prevents arterial inflammation and protects arteries through G protein-coupled receptor MASR ,providing both anti-inflammatory and anti-fibrotic properties. In a study, involving ACE2 gene deletion, young mice did not show any gross kidney abnormalities, and the cortex and medulla of their kidneys appeared normal. However, Electron microscopy revealed signs of mesangial damage, characterized by small areas of fibrillar collagen deposition, suggesting an early stage of the disease. In contrast, adult mice with ACE gene deletion showed diffuse glomerular sclerosis, hyalinosis, mesangial expansion, and albuminuria.

Moreover, immunohistochemical assessment revealed elevated staining of fibronectin, collagen I and III, and smooth muscle α-actin (23). Another study reported hypertension, glomerular damage, and renal fibrosis in diabetic mice with deleted ACE2 gene. Autopsy specimens taken from renal tissue of patients afflicted by SARS-COV-2 have confirmed the presence of acute proximal tube damages, including loss of brush border, dilatation of the tubular lumen with cellular debris, vascular destruction, necrosis at some times, and epithelial dissociation and loss of tubular basement membrane. Indeed, viral particles bodies have been observed using an electronic microscope in peri-tubular space and endothelial cells of glomerular capillary rings (24). In patients with type 2 diabetes and diabetic nephropathy, decreased ACE2 and increased ACE expression levels are observed in glomeruli and tubules,leading to dramatically increased ACE/ACE2 ratio. A study demonstrated that elevated ACE2 mRNA levels in diabetic kidneys might elevate the risk or severity of infection of the kidney with SARS-CoV-2. Treatment with recombinant human ACE2 reduces the rise in albumin excretion in diabetic rats and slows the progression of diabetic kidney disease (25).

2.6. Multifaceted Roles of ACE2 In The Brain:

From Neuroprotection To COVID-19 Neurological Manifestations

Numerous animal models have been employed to investigate the diverse roles of ACE2 in the brain. Studies have demonstrated that ACE2 exerts antihypertensive and sympatholytic effects in the hypothalamus by reducing angiotensin II concentrations and elevating angiotensin-(1-7) levels. Additionally, ACE2 plays a neuroprotective role in stroke recovery. ACE2 also participates in memory mechanisms by regulating brain-derived neurotrophic factor (BDNF) expression and reactive oxygen species production, in stress regulation through modulating corticotropin-releasing hormone (CRH) levels at the hypothalamus, and in neurogenesis mediated by serotonin levels, which are secondary to the presence of its precursor, tryptophan. The interaction between tryptophan production and ACE2 function spans across multiple systems, intertwining their functional contributions. For instance, ACE2, involved in RAS-mediated homeostasis, also contributes to the regulation of microbiota, amino acid absorption, and antimicrobial peptide production at the intestinal level (26).An increasing body of evidence indicates that individuals with COVID-19, especially those experiencing severe illness, exhibit neurological signs. This suggests the potential for SARS-CoV-2 to infect and harm neurons within the central nervous system (CNS) of humans.

Studies using neurons derived from human pluripotent stem cells have revealed ACE2 expression in these neurons through immunocytochemistry. This finding highlights the potential for SARS-CoV-2 to invade the nervous system and the probability that infected neurons can impair respiratory function. This raises the possibility that respiratory failure in severe COVID-19 patients may be amenable to treatment from the CNS perspective. In another study, Hernández et al. (2021) investigated the expression and distribution of ACE2 in specific cell types within the rat brain. Their findings indicated that identifying neurons expressing ACE2 in the brain of rats within well-established functional circuits could aid in predicting potential neurological manifestations associated with dysregulation of ACE2 in the brain during and after COVID-19 infection (27).

2.7. Role of ACE2 In COVID-19-Related Gastrointestinal And Pancreas Manifestations

ACE2 plays an essential role in the gastrointestinal (GI) tract and pancreas, and its dysregulation has been implicated in the development of gastrointestinal and pancreatic complications correlated with COVID-19 infection. In the GI tract, ACE2 acts as an amino acid transporter, regulating the uptake of tryptophan, an essential amino acid involved in various physiological processes. Animal studies have shown that ACE2 deficiency leads to reduced tryptophan levels in the blood, resulting in enhanced colonic inflammation, vascular alterations, and impaired damage response mediated by the mammalian target of the rapamycin (mTOR) pathway (28). The expression of ACE2 is particularly high in the small intestine, where it is abundantly present in enterocytes, the main functional cells lining the intestinal lumen. This high expression suggests that ACE2 has a key role in maintaining the integrity of the intestinal epithelium and regulating nutrient absorption. In contrast, ACE2 expression is low in the colon, which may contribute to the enhanced colonic inflammation observed in ACE2 deficiency. Recent studies have revealed that SARS-CoV-2, the causative agent of COVID-19, could directly infect enterocytes and replicate within the GI tract. This direct invasion of enterocytes is supported by the observation that SARS-CoV-2 could be identified in stool samples of approximately half of infected individuals, even after testing negative for COVID-19 in the upper respiratory tract. The presence of SARS-CoV-2 in the gastrointestinal tract may play a role in the onset of gastrointestinal symptoms, such as nausea, anorexia, diarrhea, and vomiting, which are commonly observed in COVID-19 patients (29).

In the pancreas, ACE2 is expressed in pancreatic acini and islets, where it influences blood pressure regulation, nitric oxide production, and tissue fibrosis. Disruption of ACE2 activity in the pancreas has been linked to the development of acute pancreatitis, a condition characterized by inflammation of the pancreas, which has the potential to be life-threatening. Additionally, ACE2 deficiency has been associated with impaired glucose tolerance and the development of type 2 diabetes, suggesting a link between ACE2 dysregulation and pancreatic beta-cell dysfunction (30). Recent reports have emphasized that SARS-CoV-2 may trigger beta-cell dysfunction and lead to new-onset type 1 diabetes in both children and adults who previously had no history of the disease (30). These outcomes propose that SARS-CoV-2 infection might have a direct or indirect impact on pancreatic beta cells, potentially leading to the development of diabetes.

Further research is needed to elucidate the precise mechanisms by which ACE2 dysregulation contributes to COVID-19-related gastrointestinal complications and pancreatic dysfunction. Understanding these mechanisms could provide insights into potential therapeutic targets and preventive strategies for COVID-19 patients.

2.8. The Role of ACE2 In Liver And Spleen Dysfunction In COVID-19

ACE2, the main receptor for SARS-CoV-2, plays a crucial role in the regulation of several physiological processes, including blood pressure, inflammation, and fibrosis. ACE2 is found in endothelial cells, bile duct cells, and perinuclear hepatocytes within the liver. Significantly, there is a correlation between insulin resistance and endothelium-dependent and insulin-mediated vasodilation. Recent RNA-seq data from the Human Protein Atlas database indicate that ACE2 is predominantly expressed in liver cholangiocytes, with hepatocytes exhibiting the next highest expression levels (31). Following experimental liver injury and in patients with cirrhosis, an increase in ACE2 expression and activity has been observed (32). This suggests that ACE2 may contribute to the development of liver dysfunction in COVID-19 patients. Hospitalized patients with confirmed COVID-19 exhibited abnormal liver test results, with over 20% showing alanine aminotransferase levels exceeding three times the upper limit of normal values (32).

Moreover, more than 20% of patients experiencing liver injury, as indicated by abnormal liver function tests, were at increased risk of progressing to severe disease. Considering the elevated expression of ACE2, it is plausible that the liver could be susceptible to direct viral invasion in individuals presenting respiratory symptoms, regardless of the presence of liver disease (32).The spleen, an important organ of the immune system, also expresses ACE2, although at lower levels compared to other organs. Studies have shown that ACE2 receptors are present in the red pulp sinus endothelium and tissue-resident CD^{169+} macrophages (33). In a mouse model of sustained coronary occlusion, enalapril, which is an ACE inhibitor, reduced the mobilization of monocytes from the spleenand consequently impeded their recruitment to the infarcted area (34). Immunohistochemical analysis of postmortem tissue samples obtained from deceased COVID-19 patients revealed the expression of ACE2 on macrophages within the spleen and lymph nodes. Additionally, viral nucleocapsid protein was detected in ACE2-positive cells, specifically CD^{169+} macrophages (35). Studies have also documented the presence of proinflammatory monocyte-derived macrophages in the bronchoalveolar lavage fluid of patients suffering from severe cases of COVID-19 (35). Patients with COVID-19 exhibit a higher prevalence of apoptotic and dead cells in spleen tissue compared to non-COVID-19 controls (35). Furthermore, the decreased oxygen levels in the blood and potential thrombosis observed in the spleen of COVID-19 patients may also contribute to extensive immune cell death (35). These findings suggest that ACE2 dysregulation may contribute to liver and spleen dysfunction in COVID-19 patients. Further research is needed to elucidate the precise mechanisms by which ACE2 dysregulation leads to these complications and to identify potential therapeutic targets.

2.9. The correlation of ACE2 expression in sensory organs and COVID-19 infection

ACE2, the main receptor for SARS-CoV-2, has been identified in the pathogenesis of COVID-19. Its expression is not only prevalent in the respiratory tract but also in sensory organs such as the eyes, ears, and oral cavity. These organs play a crucial role in filtering, warming, and humidifying inhaled air, making them potential entry for viral entry. The nasal cavity and turbinates, which play a critical role in filtering and humidifying inhaled air, exhibit high ACE2 expression, suggesting that the nasal cavity is a primary entry point for SARS-CoV-2. Indeed, olfactory dysfunction, including loss of smell, cacosmia (distorted smell), phantosmia (smelling things that are not present), nasal obstruction or rhinorrhea, and nasal congestion, is a frequent symptom of COVID-19 infection (36).

ACE2 expression has also been detected in the oral cavity, particularly on the tongue, which may explain the occurrence of taste disturbances (hypogeusia/ageusia) in COVID-19 patients, particularly women and younger individuals. In some cases, loss of taste has been correlated with oral lesions. Ocular abnormalities, including conjunctivitis, have been reported in up to 31% of SARS-CoV-2 hospitalized patients. A study by Wu et al. found that ocular abnormalities were more common in worse and severe COVID-19 patients. Additionally, retinal abnormalities, such as enlargement of retinal arteries and veins, have also been linked to COVID-19 severity. The expression of ACE2 and TMPRSS2 on corneal cells suggests the potential for the virus to traverse the ocular surface and spread to other anatomical regions (36).

Expression of ACE2 has also been observed in the skin, where it plays a role in controlling cell proliferation and differentiation. Immunohistochemical studies has shown ACE2 in the basal cell layer of healthy skin and sebaceous glands. In contrast, reduced ACE2 reactivity has been observed in patients with premalignant lesions and non-melanoma skin malignancies. This suggests that ACE2 may play a role in the pathogenesis of these skin diseases (37). Skin manifestations, including non-pruritic erythematous rashes, urticaria, or lesions resembling varicella, have been observed in patients with COVID-19. However, it remains uncertain whether these skin manifestations indicate viral replication at the site or are local reactions to systemic infection. Further research is needed to elucidate the precise role of ACE2 in sensory organs and COVID-19 infection (36).

2.10. ACE2 and Reproductive Systems: Insights Into COVID-19 Infection

The presence of ACE2 in the reproductive systems, particularly in the testes and ovaries, has raised concerns about the potential impact of SARS-CoV-2 infection on these organs. This concern originates from the observation that ACE2 serves as the primary receptor for SARS-CoV-2, allowing the virus to gain entry into host cells. Angiotensin II, the biological product of ACE2, plays a crucial role in regulating reproductive functions throughout the menstrual cycle and pregnancy.

In the female reproductive system, AngII influences follicular development, oocyte maturation, corpus luteum progression, and spiral artery vasoconstriction, thereby maintaining hormonal balance and supporting the endometrium regeneration process. During pregnancy, the ACE2/AngII/Ang 1–7 axis plays a critical role in blood pressure regulation. Alterations in this pathway have been linked to complications, such as preeclampsia and eclampsia, while reduced ACE2 expression can negatively impact fetal development and birth outcomes (36). In the male reproductive system, ACE2 is expressed in spermatogonial cells, Leydig cells, and Sertoli cells, potentially influencing spermatogenesis and maintaining the structural and functional integrity of the reproductive apparatus. Research has indicated significant expression levels of ACE2 in different reproductive organs, including the spermatids, testes, fallopian tubes, ovaries, placenta, and uterus, implying a potential susceptibility of these organs to SARS-CoV-2 infection. Indeed, SARS-CoV-2 has been detected in the testes of infected individuals, and a post-mortem analysis of 91 COVID-19 fatalities showed different degrees of reduction and damage to spermatogenic cells, alongside the presence of SARS-CoV-2 RNA and virus particles in the testes. Furthermore, several studies have documented testicular discomfort and parenchymal damage in COVID-19 patients, even in cases where the testes did not test positive for SARS-CoV-2 (36).

Considering the role of AngII, ACE2, and Ang-(1–7) in regulating female reproductive functions, SARS-CoV-2 infection could disrupt these processes, potentially leading to infertility, menstrual irregularities, and fetal distress. Pregnant women infected with COVID-19 are potentially at risk for preterm delivery. Recent evidence has highlighted cases of preeclampsia and gestational hypertension among COVID-19-positive pregnant women. Additionally, trophoblastic cells, which directly interface with maternal blood in the intervillous space, exhibit notable expression of ACE2 during pregnancy. This finding suggests the plausibility of SARS-CoV-2 infecting the placenta through a receptor-mediated mechanism. A study examining potential transmission routes during the first trimester identified ACE2 expression,along with concurrent TMPRSS2 expression, in the trophoblast, blastocyst, and hypoblast. However, other proteases, including Furin, trypsin, and cathepsins B and L, may also contribute to SARS-CoV-2 entry into the placenta (36). In conclusion, the presence of ACE2 in the reproductive systems and its association with SARS-CoV-2 infection highlight the potential risk posed by this virus to these organs. Further research is needed to fully elucidate the mechanisms by which SARS-CoV-2 can affect reproductive health and to develop strategies to reduce these risks.

2.11. ACE2 in The Thyroid And COVID-19 Implications

ACE2 expression has been observed to be elevated within thyroid tissues. Enrichment analysis of thyroid tissue revealed an inverse correlation between ACE2 expression and the abundance of killer T cells (CD^{8+}) in the females. Conversely, a significant positive association was identified between ACE2 expression and interferon response makeup in the males. Moreover, no gender- or age-related differences in ACE2 expression were detected in various other tissues. ACE2 plays a critical role in thyroid dysfunction and the progression of certain neoplasias.

Hypothyroidism or hyperthyroidism, conditions associated with insufficient or excessive thyroid hormone

(TH) production, respectively, may influence ACE, AngII, and Ang 1–7 levels. Studies have shown that overactive thyroid glands exhibit elevated plasma levels of ACE or AngII , while hypothyroidism tends to reduce these levels (38). Direct thyroid involvement has been linked to COVID-19, with cases of subacute thyroiditis reported in conjunction with mild COVID-19. However, subacute thyroiditis is not the sole thyroid condition linked to COVID-19. Instances of thyrotoxicosis induced by thyroxine have also been documented. Several studies have delved into the occurrence of subacute thyroiditis and thyroxine-induced thyrotoxicosis in cases with severe COVID-19 requiring intensive care unit admission. Recently, a retrospective analysis of 50 COVID-19 patients revealed a reduction in total T3 and thyroid-stimulating hormone (TSH) levels in 56% of the patients. The decline in T3 was particularly pronounced in cases with severe SARS-CoV-2 infection. Previous findings have suggested that expression levels of ACE2 are heightened in the thyroid and exhibit positive and negative correlations with immune signatures in both females and males. Moreover, TMPRSS2, another enzyme involved in SARS-CoV-2 entry into cells, is expressed in the thyroid. These findings suggest that the thyroid gland may be involved in SARS-CoV-2 infection. Further studies are needed to clarify the mechanisms by which SARS-CoV-2 affects thyroid function and to develop strategies to mitigate these effects (36).

2.12. ACE2 in Bone Marrow And Potential Links To COVID-19

ACE2 is locally expressed in human bone marrow-derived stem/progenitor cells (BMSPCs), influencing cytokine signaling that promotes skeletal repair. Literature has also demonstrated that osteoclasts and osteoblasts express ACE2/MAS, highlighting the role of the ACE2/Ang-(1–7)/Mas axis in regulating the metabolism of bone. Activation of the ACE2/Ang-(1–7)/MAS axis inhibits bone resorption and exerts anti-inflammatory properties. In postmenopausal animals, the ACE-2/Ang1-7/Mas axis acts as a helpful RAS axis to promote osteoprotective impacts, proposing that ACE2 is crucial for preserving the structure of bone. ACE2 deficiency has been shown to worsen diabetes-induced bone marrow microenvironment, associated with impaired migration and proliferation of BMSPCs (39).

Preliminary clinical data have revealed that COVID-19-is associated calcium metabolic disorders and osteoporosis. Notably, severe COVID-19 cases exhibit significantly reduced levels of blood phosphorus and calcium compared to moderate COVID-19 cases. These findings raise the possibility of a relationship between SARS-CoV-2 infection and skeletal system damage. Osteoclasts, responsible for bone resorption, develop from fused bone marrow-derived macrophages (BMMs) under the influence of macrophage colony-stimulating factor (M-CSF) and receptor activator of nuclear factor Kappa-B ligand (RANKL). The controlled differentiation of BMMs into osteoclasts is crucial for preserving skeletal homeostasis. During SARS-CoV-2 infections, macrophages play a crucial role in immune response. However, dysregulated macrophage activation can accelerate progression of the disease. While, in COVID-19 patients, macrophages from lymph node subcapsular and splenic marginal zones express ACE2, most tissue-resident macrophages from humans exhibit low ACE2 expression, particularly in bone marrow cells (40). Despite the low expression of ACE2 in bone marrow cells, the possible role of ACE2 and BMMs in SARS-CoV-2-induced skeletal damage needs further investigation. Further research is needed to elucidate the mechanisms by which SARS-CoV-2 disrupts bone metabolism and to develop strategies to mitigate these effects (41).

In summary, the ACE2 receptor exists in different body tissues and plays an important role in physiological conditions. One of the most important roles of ACE2 in the body's physiology is the regulation of the RAS, which controls the regulation of blood pressure, fluid and electrolyte balance, cardiovascular function, and overall body health. Also, ACE2 plays a role in protecting lung tissues and controlling inflammation. In addition, the ACE2 receptor plays a role in the infection and persistence of the SARS-CoV-2 virus, the main cause of the COVID-19 disease. The virus initiates infection by attaching to the ACE2 receptor on cell surfaces, which allows it to enter the cell. Therefore, the presence of ACE2 receptor in different tissues of the body can lead to COVID-19 infection, especially in the lungs, which is one of the main environments for the virus to proliferate. The physiological and the pathological role of this receptor in the presence of SARS-CoV-2 in different tissues are shown in Figure 2.

2.13. Exploring RAS modulation in COVID-19 management: a focus on ACE2 receptor

The RAS plays a crucial role in regulating blood pressure, fluid and electrolyte balance, and cardiovascular

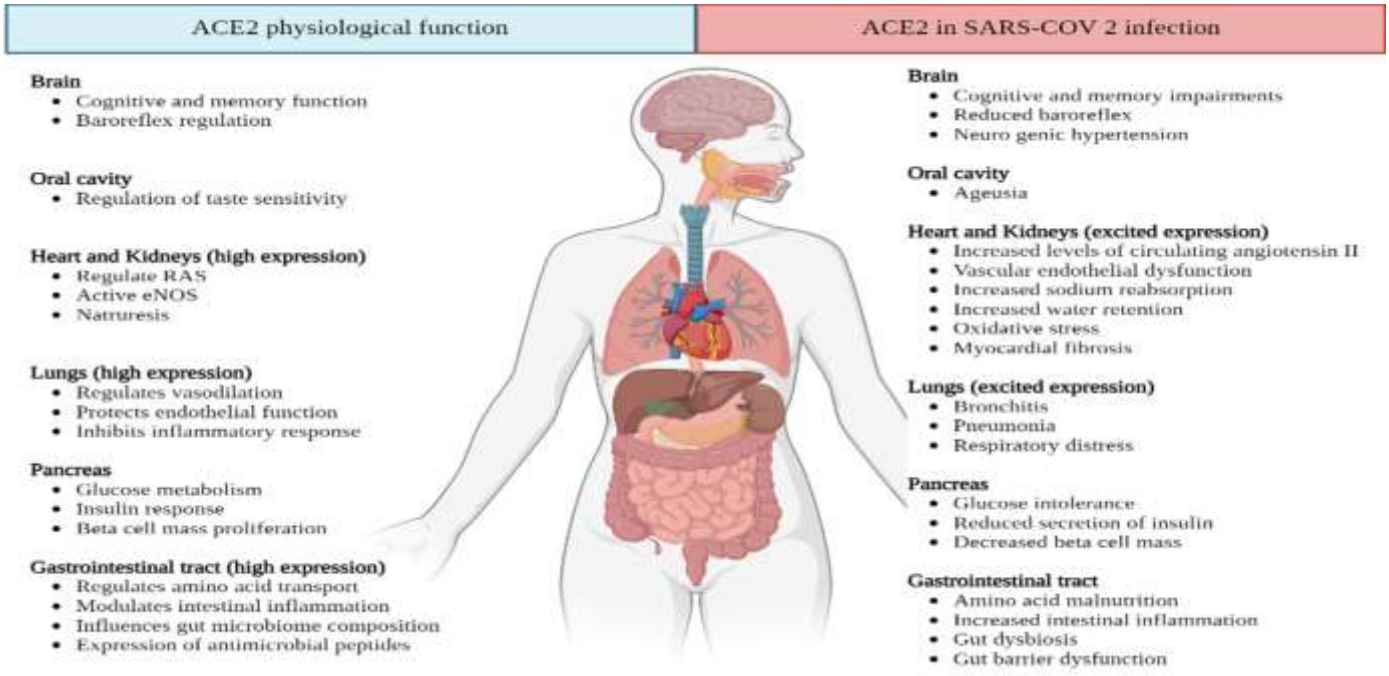

Figure 2. The Angiotensin-converting enzyme 2 (ACE-2) function in physiological conditions and SARS-CoV-2 infection. The figure shows the varying levels of ACE2 expression in normal organs. This figure provides an overview of normal ACE2 function and the potential consequences of ACE2 disruption caused by SARS-CoV-2 infection. ACE2 is crucial for normal physiological functions in different tissues. Disruption of ACE2 by SARS-CoV-2 binding may lead to short- and long-term pathophysiological effects on organ systems that rely on ACE2 for proper function. This figure was adapted from Salamanna et al. 2020 (1).

function. With the emergence of the COVID-19 pandemic caused by the novel coronavirus SARS-CoV-2, there has been considerable interest in the potential role of RAS-modulating drugs in managing the disease. However, the reduction of ACE2 levels can lead to an increase in Ang, potentially triggering detrimental effects on blood pressure, inflammation, thrombosis, and lung function.

In addition, variations in the ACE2 gene and its expression levels may influence how SARS-CoV-2 affects host cells. Yet, it is important to recognize that ACE2 gene expression and genetic variations are not the only factors involved. Environmental and genetic factors, including those related to both innate and adaptive immune responses, can significantly affect disease outcomes (42). Studies have been conducted to assess the efficacy of recombinant human ACE2 in SARS-CoV-2-infected patients.Administering ACE2 may competitively bind to SARS-CoV, thereby preventing the viral spike protein from binding to full-length membrane ACE2 and consequently reducing viral cell entry. Intravenous administration of recombinant ACE2 holds promise in preventing pulmonary arterial hypertension and acute lung injury (14). Additionally, TMPRSS2 protease inhibitors have shown efficacy in blocking SARS-CoV-2 entry into host cells. Camostat mesylate, a serine protease inhibitor commonly used in chronic pancreatitis treatment, inhibits TMPRSS2. In vitro studies demonstrate its ability to impede viral entry into bronchial epithelial cells, suggesting potential therapeutic benefits (8).

Zhang et al. conducted a multi-center study involving 1128 adult patients with COVID-19 and hypertension, including 188 patients receiving ACEIs and ARBs (ACEI/ARB group; and 940 not using ACEI/ARB (non-ACEI/ARB) group. Patients were hospitalized at 9 hospitals in Hubei Province, China, from December 31, 2019, to February 20, 2020. Using a mixed-effect Cox model with the site as a random effect and adjusting for variables such as age, gender, comorbidities, and in-hospital medications, the study observed a lower risk of all-cause mortality among patients in the ACEI/ARB group compared to the non-ACEI/ARB group.

After conducting propensity score-matched analysis and adjusting for imbalanced variables in a mixed-effect Cox model, consistent findings indicated a reduced risk of COVID-19 mortality in patients receiving ACEI/ARB

compared to those not receiving them. Furthermore, subgroup analysis based on propensity score matching revealed that ACEI/ARB usage was associated with decreased mortality in COVID-19 patients with concurrent hypertension compared to other antihypertensive drugs (43).Garcia et al. conducted a placebo-controlled ,randomized clinical trial across 13 hospitals in the United States from April 2020 to February 2021. The study targeted hospitalized COVID-19 patients with a respiratory sequential organ failure assessment score of at least 1 who were not currently receiving treatment with a RAS inhibitor. Patients were eligible for participation if they met these criteria. The trial compared the administration of Losartan 50 mg orally twice daily to an equivalent placebo, for 10 days or until the patient was discharged from the hospital. The main outcome measured was the calculated arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2:FiO2) ratio after 7 days. Secondary endpoints included the severity of COVID-19 (categorized by ordinal numbers), the duration without the need for supplemental oxygen, mechanical ventilation, or vasopressors, and mortality rates. Additionally, Losartan pharmacokinetics and components of the RAAS, including angiotensin II (AII), angiotensin-[1-7], and angiotensin-converting enzymes 1 and 2, were assessed in a participants subgroup. A total of 205 participants were randomized, with 101 assigned to the Losartan group and 104 to the placebo group. The study found that Losartan did not significantly influence the PaO2:FiO2 ratio at 7 days compared to placebo.

Furthermore, Losartan did not improve secondary clinical outcomes and resulted in fewer vasopressor-free days compared to placebo (44).

Azithromycin exhibits high binding affinity to the SARS-CoV-2 spike protein, potentially disrupting its interaction with ACE2, which is crucial for viral entry. It also reduces inflammation and viral replication by modulating immune responses and decreasing metalloproteinase expression. However, azithromycin can cause gastrointestinal issues, headache, and dizziness, and has severe risks such as QT prolongation, especially when combined with hydroxychloroquine. Hydroxychloroquine (HCQ) and chloroquine (CQ) interact with ACE2, potentially reducing the viral entry into cells. HCQ is less toxic than CQ but carries risks such as QT prolongation and retinal toxicity. Clinical trials have shown limited benefits of HCQ in treating COVID-19, leading to its discontinuation by the WHO due to a lack of significant impact on mortality. NSAIDs like ibuprofen might increase ACE2 expression, raising concerns about worsening COVID-19 symptoms, though the European Medicines Agency found no firm evidence linking NSAIDs to adverse COVID-19 outcomes. Paracetamol is recommended instead, as NSAIDs can have nephrotoxic effects. Zinc plays a role in modulating viral entry and replication. It supports respiratory health and enhances immune responses.

Zinc supplementation could be beneficial in COVID-19 therapy; though excessive intake should be avoided. Vitamin D influences ACE2 expression and might offer protective benefits in COVID-19 by reducing ACE2 levels in certain contexts, though its role in direct antiviral activity is less clear. Remdesivir inhibits viral replication and might block SARS-CoV-2 binding to ACE2. It has shown safety in clinical trials, suggesting it could be an effective treatment for COVID-19 (45).

4. Conclusion

This review highlights the complex relationship between COVID-19 and ACE2 across various tissues, emphasizing mechanisms that contribute to adverse disease outcomes. Tissue abnormalities associated with COVID-19 can manifest during both acute and recovery phases, potentially due to direct infection or autoimmune responses triggered by cytokine storms. ACE2 plays a key role in SARS-CoV-2 infection and its effects. Targeting ACE2 could help reduce viral entry and manage COVID-19 symptoms. Further research is needed to enhance the understanding, diagnosis, and management of COVID-19-related disorders. While considering recombinant ACE2 therapies, we advocate for ongoing assessment of ACE2 function in patients during and after COVID-19, particularly. Future research should focus on optimizing ACE2-based treatments, including developing ACE2 mimics or analogs that offer increased stability and prolonged circulation. Identifying agents that modulate ACE2 expression or activity could enhance its protective role or prevent its reduction in severe cases. Combining ACE2-targeted therapies with other treatments, such as antivirals and immunomodulators may provide additional benefits. While the prospects for ACE2-based therapies are promising, ongoing research and collaboration are crucial for maximizing their potential and improved patient outcomes.

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Authors' Contribution

Study concept and design: MK.
Acquisition of data: MK, MB, and AHM.
Analysis and interpretation of data: MK, and AHM.
Drafting of the manuscript: MK, and AHM.
Critical revision of the manuscript for important intellectual content: MK, and AHM.
Statistical analysis: Not applicable.
Administrative, technical, and material support: MK.
Study supervision: MK, and AHM.

Ethics

Ethical approval is not applicable for this type of study.

Conflict of Interest

The authors declare no conflicts of interest.

Data Availability

Not applicable.

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