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The Potential Role of Renin Angiotensin System (RAS) and Dipeptidyl Peptidase-4 (DPP-4) in COVID-19: Navigating the Uncharted

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Abstract

Novel coronavirus (COVID-19) led to infected pneumonia and acute respiratory distress syndrome (ARDS) and acute kidney injury (AKI). The entry-point receptor for COVID-19 is angiotensin-converting enzyme 2 (ACE2) at lung, and dipeptidyl peptidase-4 (DPP-4) is a receptor for Middle East respiratory syndrome coronavirus (MERS-CoV). There is 80% similarity between MERS-CoV and COVID-19. This study was planned to review the potential link between the incidence and severity of COVID-19 regarding the modulation of DPP-4 and ACE2 by DPP-4 and renin angiotensin system (RAS). In COVID-19, SARS-CoV2 binds ACE2 which is highly expressed by the epithelial cells of the blood vessel, intestine, and lung. However, pulmonary ACE2 seems to be a protective defense pathway during ARDS. DPP-4 is not concerned with the entry of COVID-19 but mediates the inflammatory reactions and cytokine storm that induced ARDS and AKI by COVID-19. The interaction between DPP4i and RAS inhibitors seem to augment the expression of AT2 receptor and ACE2 which are under extensive researches to find the pathophysiological pathway of COVID-19 infection. This beneficial interaction between DPP4i and RAS shed light for possible attenuation of COVID-19-induced ARDS and AKI mainly in critically ill patients with systemic hypertension.

Keywords: COVID-19, angiotensin-converting enzyme 2, dipeptidyl peptidase-4, acute respiratory distress syndrome, acute kidney injury

1. Introduction

Coronavirus (CoV) is a positive-sense single-strand RNA genome, which is the largest known RNA virus, constitutes *Riboviria* of *Coronaviridae* family and

Orthocoronavirinae subfamily with a genome size of 27–34 kilobases. The name coronavirus is derived from the Latin word corona, meaning crown or halo, which is the feature appearance under electron microscope. Regarding COVID-19, it is similar to the other RNA viruses with additional endoribonuclease and exoribonuclease terminal caps (**Figure 1**) [1].

Formerly different researches were done to identify the cause of obscure respiratory tract infections. The identified novel agents were severe acute respiratory syndrome coronavirus (SARS-CoV) and human coronavirus NL63 (HCoV-NL63) [2]. CoV causes human acute respiratory infection in about 5–30% of the total respiratory infection. In the past, between 2002 and 2003, an epidemic had been shown caused by SARS-CoV, which causes severe acute respiratory syndrome in 8000 subjects with 750 deaths. SARS-CoV is a second coronavirus group, while HCoV-NL63 is called group 1 coronavirus [3, 4].

On December 2019, a number of cases with a novel coronavirus (COVID-19) led to infected pneumonia in Wuhan in central China. Four cases with pneumonia of unknown etiology were reported on 29 December 2019, which heralds the similar outbreak of 2003 SARS-CoV [5].

At this time, no vaccines or effective antiviral agents are approved for the treatment or prevention of human COVID-19. Therefore, the emergence of COVID-19 is regarded as a priority by the World Health Organization (WHO), Center for Disease Control and Prevention (CDC), and health agencies for the developing a therapeutic effective drug against COVID-19. In general COVID-19 as other positive-sense RNA virus is characterized by high genetic plasticity and mutations due to short replication time, with a higher rate of recombination. These criteria limit and challenge for discovering novel antiviral agents [6, 7]. However, nucleotide and nucleoside analogue inhibitors (NIs) may be an effective agent by the reduction of genetic mapping of COVID-19 [8]. NIs such as ribavirin, remdesivir, and beta-D-N4-hydroxycytidine could be effective agents despite emergence of rapid resistance [9].

Previously, it has been reported by Li et al. [11] and Kuba et al. [10] that the entry-point receptor for SARS-CoV is angiotensin-converting enzyme 2 (ACE2) at the lung [10, 11]. Besides, Eckerle et al. reported that dipeptidyl peptidase-4 (DPP-4) which cluster of differentiation 26 (CD26) is widely expressed on the surface of human cells which acts as a receptor for Middle East respiratory syndrome coronavirus (MERS-CoV) [12]. Since there is a 80% similarity between MERS-CoV and SARS-CoV with SARS-CoV-2, this study was planned to review

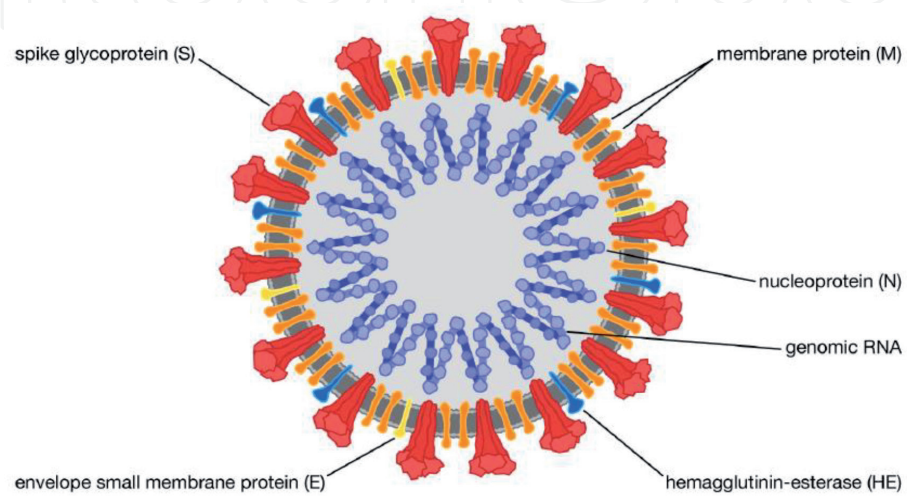


Figure 1.
Structure of SARS-CoV2.

the potential link between the incidence and severity of COVID-19 regarding the modulation of DPP-4 and ACE2 by DPP-4 and renin angiotensin system (RAS) inhibitors, respectively.

2. Literature search strategy

In general, an endeavor of this study article was to present a mini review concerning DPP-4 and RAS and their inhibitors in relation to the incidence and severity of COVID-19. Evidences and substantiations from experimental, preclinical, and clinical studies are assessed, given the nature and character of the subject area; it remains clear that this literature search cannot be considered as a systemic review. A multiplicity and array of search policy took on and are assumed, which is integrated by electronic database searches of Scopus, Web of Science, Medline, Cochrane Central Register of Controlled Trials (CCTR), and PubMed using MeSH terms, keywords, and title words during the search. The terms used for these searches were as follows: COVID-19 or coronavirus or SARS-CoV-2 and DPP-4 OR renin angiotensin system; COVID-19 or SARS-CoV-2 and DPP-4 inhibitors or sitagliptin, vildagliptin, and insulin resistance; incidence of COVID-19 or coronavirus or SARS-CoV-2; and hypertension or orphan drugs or glucagone-like peptide 1 (GLP-1) or dipeptidyl peptidase-IV inhibitors (DPPIV) or thiazolidinediones (TZDs).

Reference lists of previous and recent notorious articles were reviewed. In addition, only English articles were measured, and case reports were also of concerned in this review. The key features of predictable and suitable search studies were considered, and the conclusions were summarized and summed up in a mini review.

3. Renin angiotensin system (RAS) and COVID-19

RAS is a signaling pathway for the regulation of blood pressure, blood volume, natriuresis, and other vascular functions [13]. RAS consists of different effector peptides that control the dynamic vascular functions. Angiotensinogen from the liver is converted to angiotensin I (AngI), which is converted to angiotensin II (AngII) by angiotensin-converting enzyme 1 (ACE1). AngII activates two types of receptors which are AT1 (vasoconstrictor) 90% and AT2 (vasodilator) 10%. The overall effect of AngII is vasoconstriction with sympathetic activation and aldosterone release. Excess of AngII is metabolized by ACE2 into vasodilator Ang (1–7) which act on specific receptor called MAS receptor (**Figure 2**). AngII can also be converted to angiotensin A by mononuclear leukocyte-derived aspartate decarboxylase (MLDAD), leading to the formation of alamandine, which has been shown to bind to the mas-related G protein-coupled receptor D [14].

In COVID-19, SARS-CoV-2 binds ACE2 which is highly expressed by the epithelial cells of the blood vessel, intestine, and lung. The expression of ACE2 is augmented by angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) (**Figure 3**) [15] as well as ibuprofen and thiazolidinediones, and cigarette smoking also increases the expression of ACE2 at epithelial cells of the lung. Therefore, hypertensive patients on ACEIs or ARBs are at higher risk for COVID-19 [16, 17].

Recently, Zhou et al. [18] found that the COVID-19 genome is 96% identical to the bat CoV, so spike glycoprotein (S protein) and receptor binding domain (RBD) of both SARS-CoV-2 and bat CoV bind ACE2, which might explain the cross-species transmission, which means from bat to human and from human to human [19]. In addition, the affinity of COVID-19-RBD to ACE2 is approximately 10–20 times more

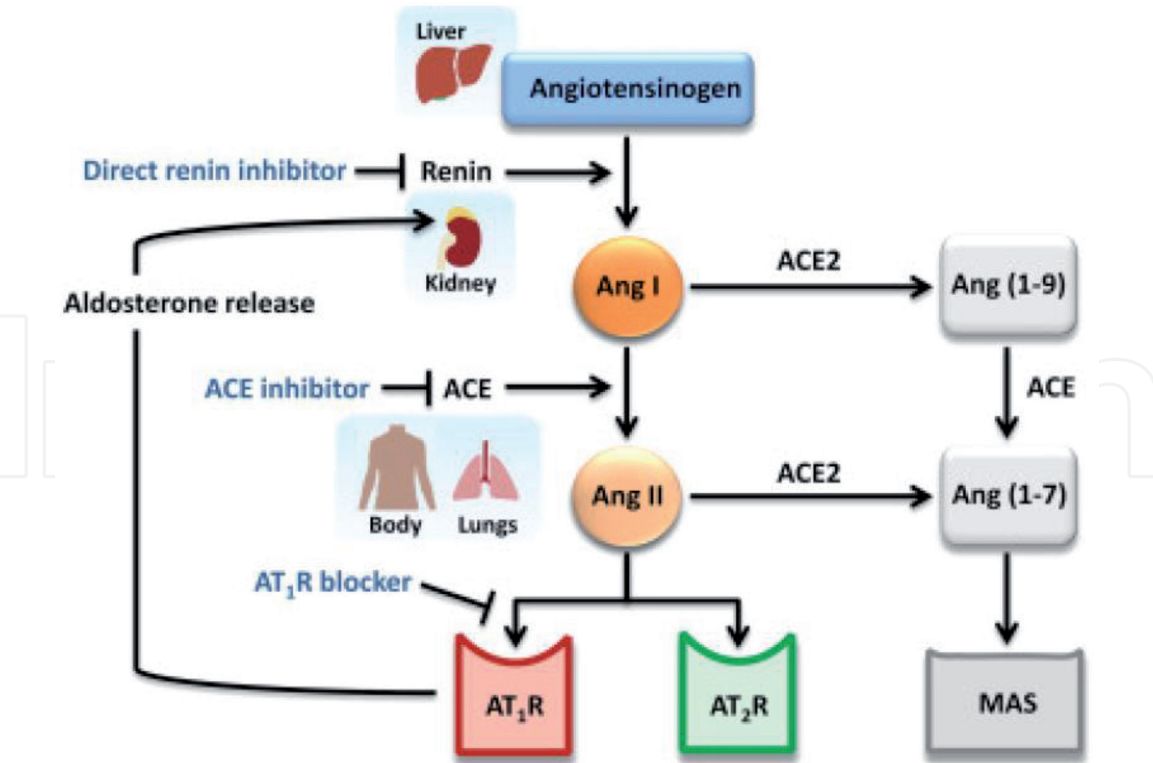


Figure 2.
Renin angiotensin system (RAS).

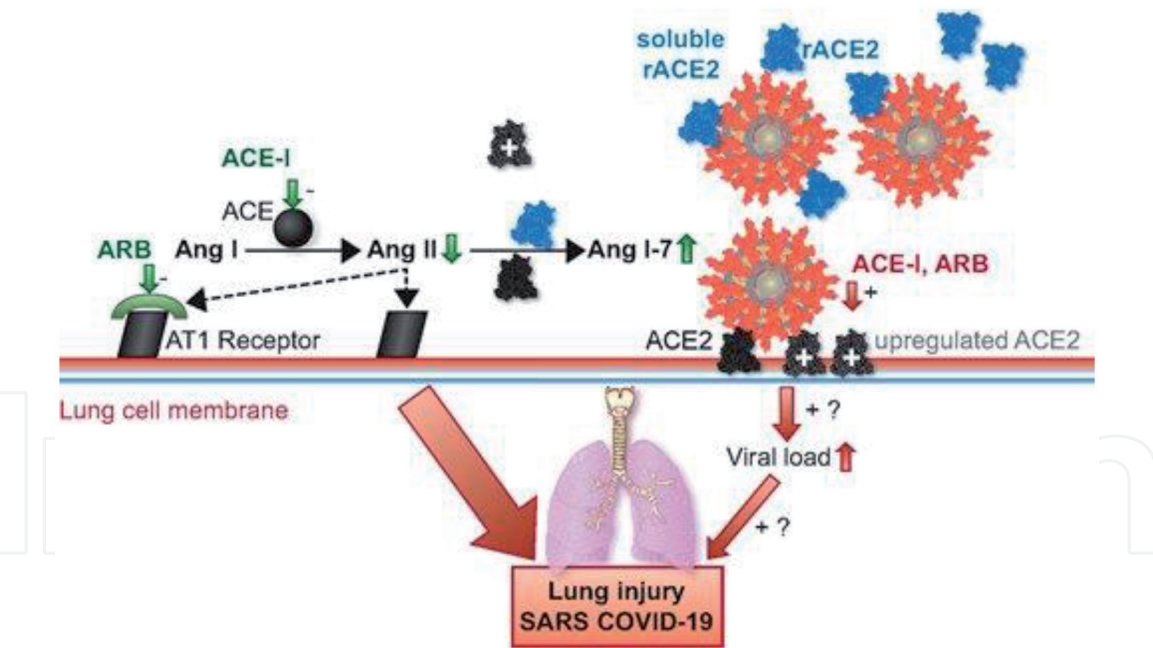


Figure 3.
Role of angiotensin-converting enzyme 2 (ACE2).

than that of SARS-CoV [20]. It has been shown that smoking upregulates ACE2 via activation of pulmonary platelet factor and induction of oxidative stress and inflammatory reactions. Increased ACE activity also contributes to impaired vascular relaxation observed in smokers. Irbesartan, an AT₁R antagonist (also known as angiotensin receptor blocker), was found to reduce arterial stiffness in hypertensive patients. When stratified by smoking status, smokers were found to have stiffer arteries before treatment, and irbesartan was able to reduce arterial stiffness to a greater extent in smokers than in nonsmokers, indicating that overactivity of

the RAS contributes to increased arterial stiffness in smokers. On the other hand, overexpression and upregulation of ACE2 is regarded as a protective measure via the reduction of pro-inflammatory cytokines mainly tumor necrosis factor (TNF- α) which is augmented in smoker subjects [21]. Therefore, active cigarette smoking subjects are at high risk for COVID-19 regardless of gender difference (**Figure 4**).

The activity of RAS is high in the lung, which is the main source of circulating AngII due to higher expression of ACE. Lung ACE2 controls the balance of RAS activation through regulating AngII/Ang 1–7 ratio. Local pulmonary AngII provokes vascular permeability, causing pulmonary edema [22]. However, in acute respiratory distress syndrome (ARDS), the activation of RAS is necessary to maintain oxygenation since ACE2 knockout mice illustrated more sever pulmonary damage than the controls. Thereby, pulmonary ACE2 seems to be a protective defense pathway during ARDS [23]. In addition, ACE2 has an important anti-inflammatory action, and so ACE2 therapy is effective in the treatment of hypertension and diabetic nephropathy through attenuation of AngII-induced inflammation and oxidative stress [24]. Even so recombinant ACE2 is effective in the management of animal model ARDS, the inhibition of ACE2 may lead to fatal outcomes due to the reduction of vasodilator Ang1–7. However, chronic intravenous administration of Ang1–7 or MAS agonists leads to vasodilatation independent of circulating AngII levels [25].

Depending on these observations, different studies illustrate that RAS inhibitors might be of value in the reduction of ARDS, respiratory failure, and acute pneumonia that are induced by SARS-CoV-2 [26]. Though Wang [27] confirms that RAS inhibitors increase the risk of COVID-19 due to the upregulation of pulmonary ACE2, this study recommends stopping RAS inhibitors during COVID-19 outbreak. Nonetheless, all recruited patients with COVID-19 developed ARDS without any evidence of AKI [27]. Thus, RAS system mainly ACE2/Ang1–7 grows to be the focus and meeting point of different researches to implicate this pathway in the pathogenesis of COVID-19.

Guo et al. found that the expression of ACE2 is higher renal tubules than in lung tissues; nevertheless COVID-19 leads to ARDS in much at higher than that of acute

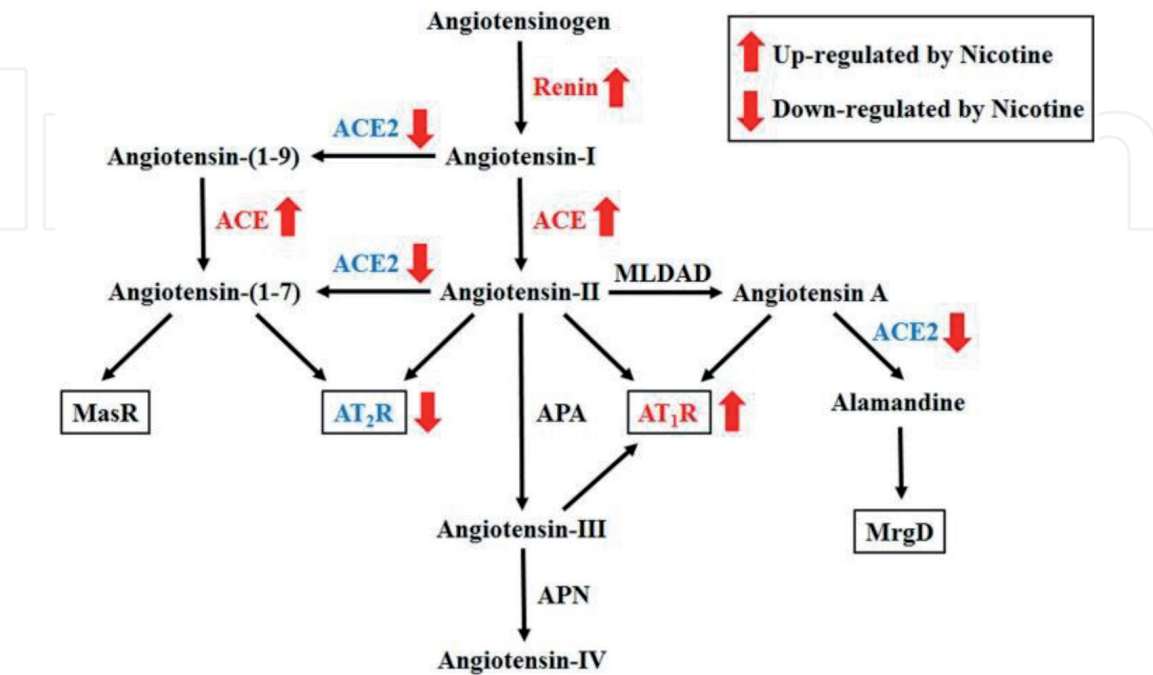


Figure 4.
Nicotine smoking and ACE2.

kidney injury (AKI), suggesting other mechanism other than ACE2 binding in the pathogenesis of COVID-19 [28]. AT2 receptor is activated by ACE2 and Ang1-7 that oppose the activity of AT1 receptor [29]. Similarly, AT2 receptors are highly expressed in lung epithelial cells compared with kidney tissues. Pulmonary AT2 receptors mediate lung injury through the augmentation of pulmonary inflammation and vascular permeability as well as the development of pulmonary fibrosis [30]. Consequently, pulmonary AT2 receptor antagonists are regarded as a novel pathway in COVID-19-induced pneumonia and ARDS. This finding does not rule out the responsibility of ACE2, since the activation of ACE2 by SARS-CoV-2 causes considerable activation of pulmonary AT2 receptors (**Figure 5**).

Amid myriad literature survey, polymorphism of ACE2 has been associated with different cardio-metabolic disorders; thus, the implication of ACE2 and AT2 receptors in COVID-19-induced pneumonia should be considerably regarded with ACE2 polymorphisms [31]. Furthermore, the expression of ACE2 might not be necessary for COVID-19 infection and viral entry, as the absence of SARS-CoV-2 in some ACE2 expressing cell types as well; this infection was observed in some cell line lacking ACE2, suggesting a vague pathway, and cofactors might be necessary for human infection [32]. Amusingly, Gurwitz [33] animal model study shows that pulmonary COVID-19 infection leads to significant lung injury through the downregulation of ACE2, which is attenuated by the administration of ARB. This study suggests the protective role of RAS inhibitors in COVID-19-induced ARDS [33]. Indeed, most of reported data from various social media during this dangerous outbreak was not legitimate due to overwhelming lay press and sparked concerns. Therefore, the high incidence of COVID-19 in patients receiving ACEIs or ARBs might be not because of these drugs but because those patients were often older, hypertensive, or diabetic which in fact increase the risk of COVID-19 infection. In addition, a recent clinical trial on the effectiveness of recombinant ACE2 (rACE) in the management of COVID-19 infection has been started [34], and we are waiting for these results. Thus, according to the guideline for the management of hypertension, RAS inhibitors should be used irrespective of COVID-19 infection, as sudden

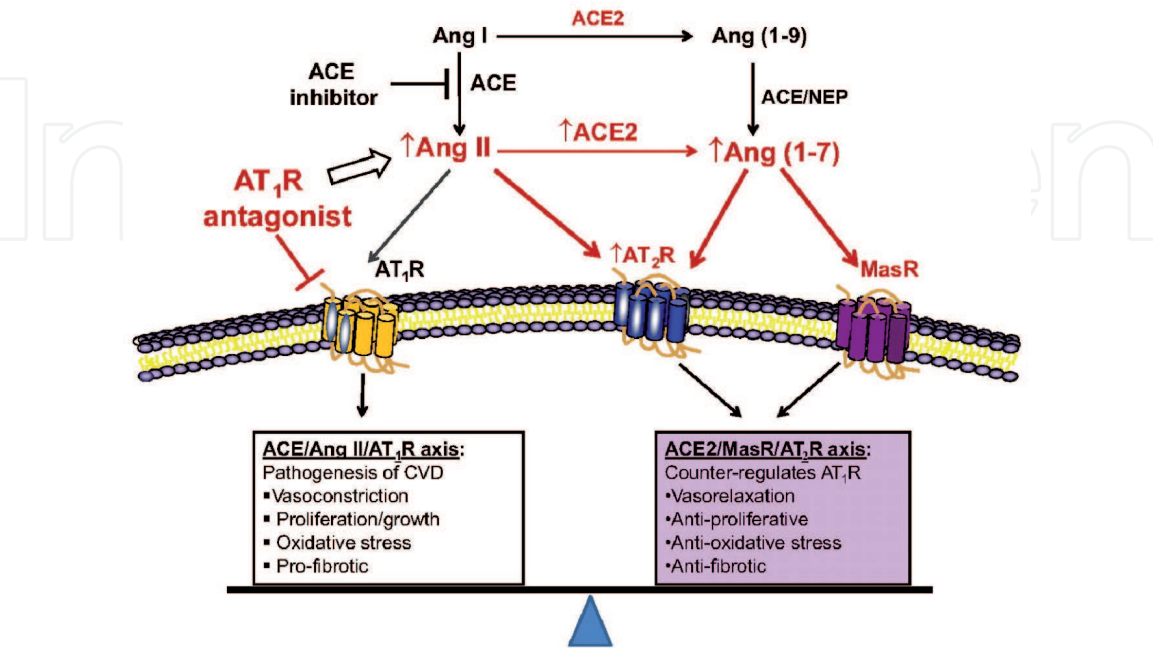


Figure 5.
Role of AT2 receptors in COVID-19.

withdrawal of these therapeutic regimens may increase the risk of deleterious outcomes in critically ill patients.

Regarding gender differences in the expression of ACE2, ACE2 gene is located on the X chromosome, which gives the possibility of gender differences in the susceptibility for COVID-19 infection. Females have lower levels of ACE2 compared with males, which gives a clue of male vulnerability to COVID-19 infection as compared with females [35]. In addition, Shenoy et al. report that estrogen attenuates AngII-induced pulmonary fibroblast proliferation due to the upregulation of

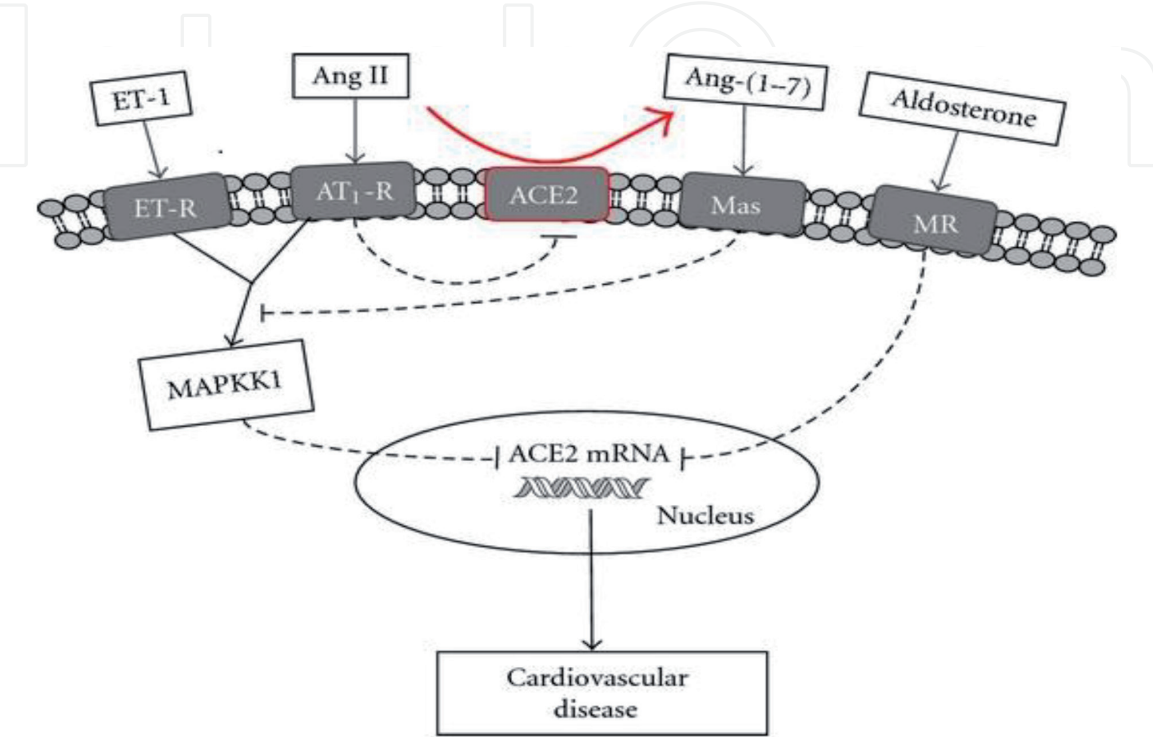


Figure 6.
Potential effects of endothelin-1 and aldosterone on the expression of ACE2.

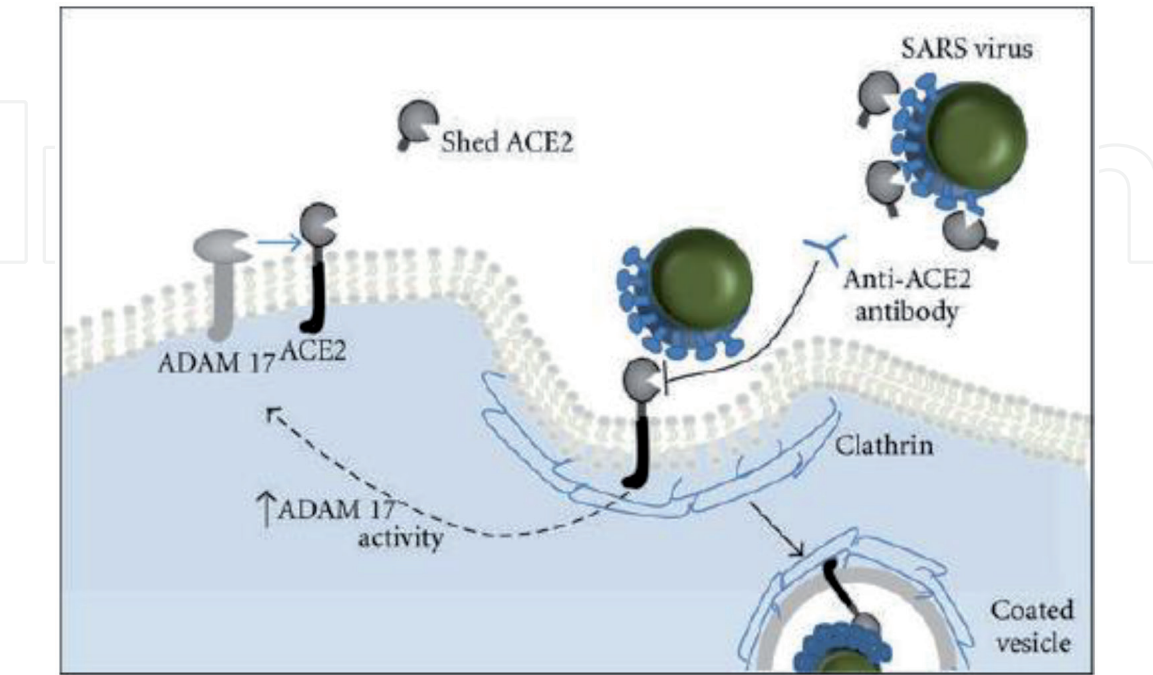


Figure 7.
Shedding of ACE2 during SARS-CoV-2 entry.

ACE2 [36]. The expression of ACE2 is regulated by different endogenous hormones and peptides; both endothelin-1 and aldosterone downregulate ACE2 expression in a rat model. So, RAS inhibitors may improve ACE2 expression via suppression of endogenous endothelin-1 and aldosterone (**Figure 6**) [37].

Moreover, ACE2 contains ectodomain and endodomain at cytoplasmic membrane; the shedding part (ectodomain) is essential for the replication of SARS-CoV-2 (**Figure 7**) [38].

At the heart of the dilemma, extensive researches are recommended to explore the specific role of ACE2 and RAS inhibitors during precarious COVID-19 world-wide outbreak.

4. Dipeptidyl peptidase-4 (DPP-4) and COVID-19

DPP4, also called adenosine deaminase complexing protein 2 (ADCP2) or adenosine deaminase binding protein (ADBP), is widely distributed on the surface of human cells. DPP4 is involved in the regulation of blood glucose, oxidative stress, inflammation, immune system, cell adhesion, and apoptosis [39]. The substrates of DPP4 are glucagone-like peptide 1 (GLP-1), stromal cell-derived factor 1 (SDF-1), brain natriuretic peptide (BNP), substance P, and neuropeptide Y (NPY). Furthermore, DPP4 interacts with different ligands such as caveolin-1, chemokine receptor type 4 (CXCR4), adenosine deaminase (ADA), and fibronectin [40].

DPP4 inhibitors (DPP4i) such as sitagliptin, saxagliptin, and vildagliptin are approved in the management of type 2 diabetes mellitus (T2DM). Additionally, DPP4i have a potential therapeutic effect regarding hypertension, endothelial dysfunction, cardioprotection, and connective tissue diseases (**Figure 8**) [41].

Regarding the role of DPP4 in viral entry and replication, Widagdo et al. [42] found that DPP4 is an important receptor for MERS-CoV transmission. DPP4 receptors are found in the human upper respiratory tract epithelium. Lacking of these receptors may restrict the transmission of MERS-CoV.

S protein of MERS-CoV binds specifically to DPP4 receptors. These interactions provoke proteolytic activation for viral entry and fusion of viral membrane with the cell membrane [43].

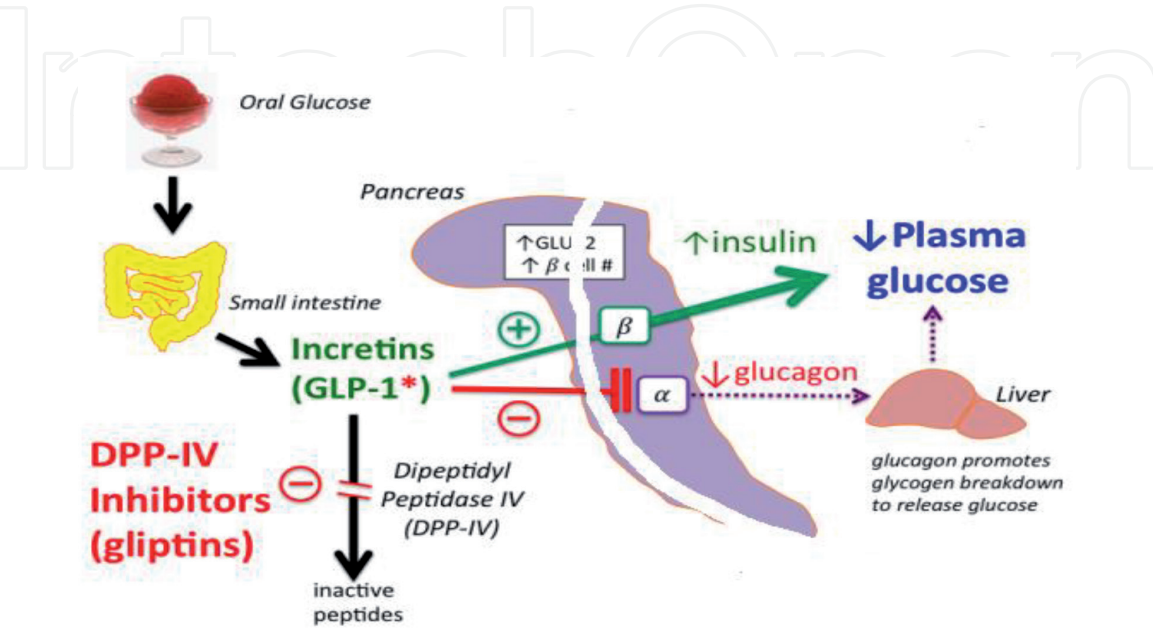


Figure 8.
Metabolic effects of DPP-4 inhibitors.

It has been observed that polymorphism in DPP4 gene is concerned with different cardio-metabolic disorders and transmission of MERS-CoV [44]. The polymorphism in DPP4 reduces the interactions between S proteins of MERS-CoV with cellular membranes. The difference in the incidence between Arabian and African MERS-CoV is mainly related to the genotype polymorphism of DPP4 [45].

Since there is a higher genomic similarity between SARS-CoV-2 and SARS-CoV, the implication of DPP4 as a receptor or a pathogenetic pathway in COVID-19-induced ARDS is reasonable. In COVID-19 infection, ARDS is developed due to massive cytokine release (cytokine storm), due to uncontrolled systemic inflammatory response, and due to the release of pro-inflammatory cytokine, including INF- α -, IL-6, IL-12, IL-33, etc., which cause multiple organ failure [46].

It has been reported that DPP4 is highly expressed on alveolar cells (type I and type II), alveolar macrophage, pleural mesothelium, and vascular endothelium. Besides, pulmonary vascular endothelial cells (PVECs) are the main source of pro-inflammatory cytokines in ARDS. DPP4 is upregulated in pneumonia, asthma, and ARDS; therefore, DPP4 inhibitors may reduce the inflammatory reaction and cytokine release in acute lung injury and ARDS through immune-modulation effect [47].

Different studies illustrated that DPP4 inhibitors inhibit the release of IL-6 and TNF- α in ARDS without effect on the blood glucose when used in a small dose [48]. Therefore, DPP4 inhibitors might be a therapeutic option in the management of COVID-19-induced ARDS.

5. The interactions between RAS and DPP4 in COVID-19

DPP4 is involved in the activation of T-cell, so the activated T-cell can synthesize and secrete AngII by local RAS. So, AngII-dependent T-cell activation is inhibited by DPP4i, leading to a significant reduction of endothelial inflammation and vasoconstriction [49]. Similarly, Bengsch et al. [50] disclosed that DPP4 receptors are highly expressed on Th17 which induced AngII release during ARDS. High circulating AngII level leads to the activation of inflammatory reactions via activation of the release of IL-18, IL-17, IL-6, and TNF- α . These mediators are essential for the induction of epithelial and endothelial cell injury during ARDS. DPP4i plays an integral role in the attenuation of IL-6 and TNF- α and associated inflammation and endothelial damage [51].

Therefore, DPP4i interferes with RAS at different levels; as teneligliptin attenuates AngII action, liraglutide downregulates AT1 and upregulates AT2 receptors during intravenous AngII infusion. Besides, exenatide inhibits the secretion of renin, AngII, and angiotensinogen [52].

What is more, DPP4i has a nephroprotective effect through the regulation of sodium and water reabsorption. Both DPP4i and GLP-1 increase sodium excretion through direct effect on proximal renal tubules or indirect effect via the activation of brain natriuretic peptide (BNP) (**Figure 9**) [53].

Consequently, DPP4i exerts protective effects on the lung and kidney which are the main tropism of COVID-19 through direct modulation of inflammatory reactions or indirectly through the attenuation of AngII. The interaction between DPP4i and RAS inhibitors seems to augment the expression of AT2 receptor which is under extensive researches to find the pathophysiological pathway of COVID-19 infection. Indeed, this interaction sheds light for possible attenuation of COVID-19-induced ARDS and AKI mainly in critically ill patients with systemic hypertension.

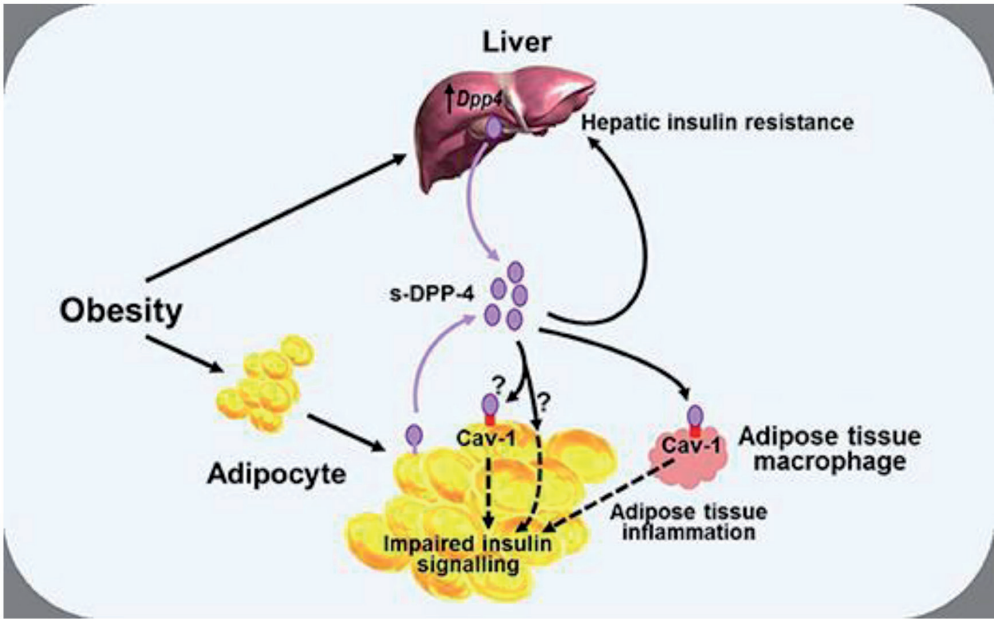


Figure 9.
Metabolic effects of DPP-4 inhibitors regarding obesity and insulin resistance.

6. Conclusion

ACE2 is regarded as a portal entry-point for SARS-CoV-2; however, human cell lines with higher expression of ACE2 are not infected by this virus. The overexpression of AT2 receptors by ACE2 and Ang1-7 is regarded as a novel pathway in COVID-19-induced pneumonia and ARDS. Females have lower levels of ACE2 than males, which give a clue of male vulnerability to COVID-19 infection as compared with females. Even so, ACE2 is regarded as a protective pathway which reduces COVID-19-induced acute inflammatory reactions. RAS inhibitors and DPP4i increase the expression of pulmonary ACE2, so the implication of RAS inhibitors and DPP4i as augmenters of COVID-19 is not practical. Therefore, addition of, DPP4i to RAS inhibitors in hypertensive patients with COVID-19 may reduce the risk of ARDS and AKI.

Conflict of interest

Nil.

Funding and sponsorship

Nil.

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