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Angiotensin converting enzyme: A review on expression profile and its association with human disorders with special focus on SARS-CoV-2 infection

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ABSTRACT

Angiotensin-converting enzyme (ACE) and its homologue, ACE2, have been mostly associated with hypertensive disorder. However, recent pandemia of SARS-CoV-2 has put these proteins at the center of attention, as this virus has been shown to exploit ACE2 protein to enter cells. Clear difference in the response of affected patients to this virus has urged researchers to find the molecular basis and pathophysiology of the cell response to this virus. Different levels of expression and function of ACE proteins, underlying disorders, consumption of certain medications and the existence of certain genomic variants within ACE genes are possible explanations for the observed difference in the response of individuals to the SARS-CoV-2 infection. In the current review, we discuss the putative mechanisms for this observation.

1. Introduction

Angiotensin-converting enzyme (ACE) has its homologue, ACE2 discovered in 2000 as a ACE related carboxypeptidase not inhibited by captopril [1,2]. ACE2 was firstly shown to be expressed in the kidneys of both the normotensive and the spontaneously hypertensive rat strains [3]. Subsequent studies demonstrated down-regulation of renal ACE2 in three different models of hypertension [4]. Moreover, circulating and cardiac levels of angiotensin II (AT-II) were shown to increase in the ACE2-null mice. ACE2 is the principal pathway for Ang-1-8 formation from AT-II (Ang-1-8), protecting against excessive activation of AT1 receptor in the heart tissues. However, newer findings suggested that ACE2 can be an important element in the renin–angiotensin aldosterone system [5]. Following these studies, ACE and ACE2 focused the attention of researchers for their contribution in diverse human disorders. Recently, the new coronavirus (2019-nCoV or SARS-CoV-2) outbreak which has affected people all over the world has further highlighted the role of ACE2. This virus has about 80% sequence identity with the severe acute respiratory syndrome (SARS)-related coronaviruses (SARS-CoVs) and 96% sequence identity to a bat coronavirus. Most remarkably, SARS-COV-2 was shown to utilize the similar cell entry receptor ACE2 as SARS-CoV [6,7]. A recent study has shown that the ACE2-binding pocket for SARS-CoV-2 spike protein receptor-binding domain (RBD) is almost identical to this one of SARS-CoV RBD. Structural protein modeling led to identification of amino acid residues in SARS-CoV-2 RBD that are critical in ACE2 binding. Notably, most of these residues are either highly conserved or have comparable side chain chemical properties with the SARS-CoV RBD. This similarity of the structure and amino acid sequence stimulated intensive debate on the convergent evolution of these viruses RBDs under a pressure of enhanced binding to ACE2 [8]. ACE2 has been shown to be expressed as a membrane bound protein in several human tissues such as lung, intestine, heart and kidney. The surface expression of this protein was demonstrated on ciliated bronchial cells and on the lung alveolar epithelial cells but also in endothelial cells, which was stated a noticeable discovery [9]. Moreover, a recent in silico analysis of RNA-seq profiles verified expression of ACE2 in the mucosa of oral cavity [10].

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**ABSTRACT**

Angiotensin-converting enzyme (ACE) and its homologue, ACE2, have been mostly associated with hypertensive disorder. However, recent pandemia of SARS-CoV-2 has put these proteins at the center of attention, as this virus has been shown to exploit ACE2 protein to enter cells. Clear difference in the response of affected patients to this virus has urged researchers to find the molecular basis and pathophysiology of the cell response to this virus. Different levels of expression and function of ACE proteins, underlying disorders, consumption of certain medications and the existence of certain genomic variants within ACE genes are possible explanations for the observed difference in the response of individuals to the SARS-CoV-2 infection. In the current review, we discuss the putative mechanisms for this observation.
Fig. 1 shows the molecular mechanisms initiated after SARS-CoVs entry into the cells and the significance of ACE and ACE2 in these processes.

In the current review, we discuss the expression pattern and function of the both ACE proteins in relation with the underlying disorders, administration of certain medications and the existence of common genomic variants within ACE genes to explain the differences in the response of affected individuals to SARS-COV-2.

2. Expression pattern of ACE and ACE2 in human disorders

In agreement with the role of ACE2 on virus uptake by cells, up-regulation of human ACE2 has increased disease severity in mice infected with SARS-CoV [15]. Moreover, injecting SARS-CoV spike into mice has led to down-regulation of ACE2, thus aggravating the lung injury [16,17]. Consequently, ACE2 functions as the cellular receptor for SARS-CoV entrance but also confers a protective mechanism against lung injury [18]. Based on these investigations, level of expression of ACE2 is an important factor in the SARS-CoV infection. Thus, comorbid conditions that influence expression of this protein might affect severity of disease. Table 1 summarizes the available data on abnormal expression of ACE and ACE2 in human/animal disorders.

Streptozotocin (STZ), immunohistochemical staining (IS), Western blot (WB), growth hormone (GH)/insulin-like growth factor-1 (IGF-1) axis, Growth hormone receptor knockout (GHR +/−) mice, major adverse cardiovascular events (MACE), Cardiovascular disease (CV), Idiopathic dilated cardiomyopathy (IDC), ischemic cardiomyopathy (ICM), Pulmonary microvascular endothelial cells (PMVECS), Recombinant human ACE2 protein (rhuACE2), Crohn’s disease (CD) and ulcerative colitis (UC).

It is worth mentioning that adult stem cells which have immunomodulatory and pro-reparative activities in the local environment [40] might affect the process of SARS infection and tissue regeneration. The regenerative capacity of these cells [41] can be exploited for avoidance of tissue damage following infection. Yet, clinical evidence in this regard is scarce. Several medications have been shown to alter expression levels of ACE or ACE2. Administration of these medications not only can modify a risk of infection with SARS-CoV, but also can affect the disease course. Table 2 summarizes the results of studies which reported alteration of ACE or ACE2 levels following administration of certain medications.

Acute Lung Injury (ALI), AXCE inhibitor (ACEI), Lipopolysaccharide (LPS), Brain of spontaneously hypertensive rats (SHR), Wistar–Kyoto (WKY), microglial cells (BV2), Streptozotocin (STZ), Rat renal tubular epithelial cells (NRK-52E), Pulmonary microvascular endothelial cells (PMVECS), Hearts of spontaneously hypertensive rats (SHR), Renal tubular epithelial cells cultured in high-glucose medium (MTC), ACE2 agonist diminazene aceturate (DIZE), Bronchoalveolar lavage fluid (BALF), Subtotal nephrectomy (STNx), Acute myocardial infarction (AMI), Sprague-Dawley rats (SD), Fasudil: Rho-associated, coiled-coil containing protein kinase (ROCK) inhibitor, Deoxycorticosterone acetate (DOCA)-salt hypertensive rat, pulmonary vascular structure remodeling (PVSR).
| Disease                | Expression/Activity | Clinical samples                                                                 | Function                                                                 | Reference |
|-----------------------|---------------------|----------------------------------------------------------------------------------|--------------------------------------------------------------------------|-----------|
| SARS-CoV infection    | ↑↑                  | Human airway epithelial cells and lung SARS-CoV 293T cells expressing ACE2 293T   | SARS-CoV preferentially infects well-differentiated ciliated epithelial 293T cells transiently over-expressing ACE2 | [19]      |
| Diabetes              | ↑↑                  | STZ-induced diabetic rats                                                         | Human (hu) 293 T kidney cells Enhanced SARS-CoV S-mediated entry into 293 T cells transiently over-expressing ACE2 293T       | [20]      |
| Hypertension          | ↑↑                  | Hypertensive human kidney/heart                                                  | Kidney tissue from 20 patients with type 2 diabetes Hyper-expression kidney/heart SHRN rats Kidney SHRN rats  SHRN rats Kidney SHRN rats | [22]      |
| Cardiac failure       | ↑↑                  | Kidney disease                                                                  | Kidney disease from 20 patients with type 2 diabetes Hyper-expression kidney/heart SHRN rats Kidney SHRN rats  SHRN rats Kidney SHRN rats | [22]      |
| Kidney disease        | ↑↑                  | 78 renal cortical specimens                                                      | Kidney disease from 20 patients with type 2 diabetes Hyper-expression kidney/heart SHRN rats Kidney SHRN rats  SHRN rats Kidney SHRN rats | [22]      |
| Acute respiratory     | ↑↑                  | Myocardial infarction rat                                                         | Myocardial infarction rat from 100 patients with type 2 diabetes Hyper-expression kidney/heart SHRN rats Kidney SHRN rats  SHRN rats Kidney SHRN rats | [22]      |
| syndrome              | ↑↑                  | Acute respiratorydistress syndrome                                              | Acute respiratorydistress syndrome from 100 patients with type 2 diabetes Hyper-expression kidney/heart SHRN rats Kidney SHRN rats  SHRN rats Kidney SHRN rats | [22]      |
| Acute lung injury     | ↑↑                  | Acute lung injury (ARDS)                                                         | Acute lung injury (ARDS) from 100 patients with type 2 diabetes Hyper-expression kidney/heart SHRN rats Kidney SHRN rats  SHRN rats Kidney SHRN rats | [22]      |
| Acute lung injury     | ↑↑                  | Acute lung injury (ARDS)                                                         | Acute lung injury (ARDS) from 100 patients with type 2 diabetes Hyper-expression kidney/heart SHRN rats Kidney SHRN rats  SHRN rats Kidney SHRN rats | [22]      |
| Acute lung injury     | ↑↑                  | Acute lung injury (ARDS)                                                         | Acute lung injury (ARDS) from 100 patients with type 2 diabetes Hyper-expression kidney/heart SHRN rats Kidney SHRN rats  SHRN rats Kidney SHRN rats | [22]      |
| Smoking               | ↑↑                  | Acute lung injury (ARDS)                                                         | Acute lung injury (ARDS) from 100 patients with type 2 diabetes Hyper-expression kidney/heart SHRN rats Kidney SHRN rats  SHRN rats Kidney SHRN rats | [22]      |
| Inflammatory bowel    | ↑↑                  | Acute lung injury (ARDS)                                                         | Acute lung injury (ARDS) from 100 patients with type 2 diabetes Hyper-expression kidney/heart SHRN rats Kidney SHRN rats  SHRN rats Kidney SHRN rats | [22]      |
| disease (IBD)         | ↑↑                  | Acute lung injury (ARDS)                                                         | Acute lung injury (ARDS) from 100 patients with type 2 diabetes Hyper-expression kidney/heart SHRN rats Kidney SHRN rats  SHRN rats Kidney SHRN rats | [22]      |
| Smoking               | ↑↑                  | Acute lung injury (ARDS)                                                         | Acute lung injury (ARDS) from 100 patients with type 2 diabetes Hyper-expression kidney/heart SHRN rats Kidney SHRN rats  SHRN rats Kidney SHRN rats | [22]      |
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Table 2
The effect of different treatments on the expression pattern of ACE and ACE2 (↑: up-regulation, ↓: down-regulation).

| Treatment | Affected protein | Treated Disease | Samples | Function | Reference |
|-----------|-----------------|-----------------|---------|----------|-----------|
| Calcitriol | – ↑              | Acute lung injury (ALI) | LPS-induced ALI rats | Calcitriol can increase the expressions of VDR mRNA and ACE2 mRNA and protein levels of VDR and ACE2. | [35] |
| – ↑        | Hypertensive brain | SHR and WKY rats/BV2 cells | Decreased Ang II, unchanged ACE and increased ACE2 suggested enhanced ACE2/Ang [1–7]/MasR axis in vivo and vitro. | [24] |
| ↓ ↑        | Diabetic kidney disease | STZ induced diabetic rats/NRK-52E cells | Regulates ACE/ACE2 possibly by p38 MAPK or ERK, but not JNK pathways. | [21] |
| ↓ ↑        | Acute lung injury (ALI) | LPS-induced ALI rats/PVH-ECs | Inhibited ACE, AT1R, induced ACE2, suppressed renin and Ang II expression. | [36] |
| ↓ ↑        | Hypertension | SHR and normotensive WKY rats | Downregulation of Ace in SHR rats and upregulation of Ace2 in normotensive WKY rats. | [42] |
| ↓ ↑        | Hepatic fibrosis | Liver fibrosis/hepatic stellate cells (HSC) | ACE inhibitors can upregulate ACE2 under conditions of liver injury both in vivo and in vitro. | [43] |
| ↓        | Myocardial infarction (MI) | Viable myocardium of MI rats | ACE inhibition was associated with inhibited cardiac ACE but ACE2 catalytic activity was unchanged. | [31] |
| ↓ ↑        | Acute kidney injury (AKI) | Renal cortex and medulla in STNx-induced AKI rats | Ramipril had no effect on ACE or ACE2 mRNA expression in either STNx or Control kidneys but increased both cortical and medullary ACE2 activity. | [44] |
| DIZE – ↑   | Hyperoxic lung injury (HLI) | BALF and lung of HLI mice | Inhibited NF-kB pathway, activated Nrf2/HO-1/NQO1 pathway and reduces severity of HLI. | [45] |
| – ↑        | Acute kidney injury | Kidney cortex of STNx rats | Increased cortical ACE2 gene expression, increased ACE2 cortex and medulla activity. Reduced cortical ACE2 activity. | [27] |
| – ↑        | Myocardial infarction (MI) | AMI rat | Suppressed TNFα, IL-6, reduced COX-2 and iNOS, and activated ACE2/AT1R/MasR pathway. | [46] |
| Statin – ↑ | Diabetic nephropathy (DN) | Kidney of DN rat | Restored ACE2 levels and further increased of AT2 receptors expression. | [47] |
| – ↑        | Thickening after vascular balloon injury | Wistar rats | Combined fluvastatin/insulin treatment more efficiently prevents diabetic cardiomyopathy. | [48] |
| ↓ ↑        | Diabetic myocardium | STZ-induced diabetic rat | Upregulation of ACE2, an increase in Ang-1–7, downregulation of AT1, and activation of the P-ERK pathway. | [49] |
| Fasudil – ↑ | Acute pulmonary embolism (APE) | SD rat PAECs | Attenuated ACE2/ACE2 ratio to normal values | [50] |
| – ↑        | Myocardial fibrosis | Overload pressure model of SD rats | ACE2 activation by ROCK inhibitor for APE treatment. | [51] |
| – ↑        | Hypertension | Hypertensive DOCA-salt rat | Fasudil inhibits overload pressure-induced myocardial fibrosis by improving ACE2 and angiotensin [1–7]. | [52] |
| – ↑        | Hypoxic pulmonary hypertension (HPH) | Hypoxia-induced FH rats/PASM | Increased vascular and plasma ACE2 activity, increased Ang II and increased Ang-1–7 plasma levels. | [53] |
| – ↑        | | | Up-regulated Ang-1–7 and ACE2, and lessened HIF-1α attenuation of the PVS and PH. | [54] |
| Gene  | SNP          | Disease                          | Treatment                                      | Case/Control | Population       | Conclusion                                    | Reference |
|-------|--------------|----------------------------------|-----------------------------------------------|--------------|------------------|-----------------------------------------------|-----------|
| ACE   | ACE I/D      | Kidney Disease and Hypertension  | ACE inhibitor ramipril                        | 347          | African American | II or DD homozygous genotypes and homozygous ACE haplotypes confer faster response to Ramipril. | [61]     |
|       |              | Hypertension                      | ACEI Enalapril, Lisinopril or Imidapril       | 190          | Japanese         | ACE-inhibitor-induced cough was not related to the ACE polymorphism. | [62]     |
|       |              | ACE-induced cough                 | ACE inhibitor                                  | 144/105      | Spanish          | The rs4646994 I allele is associated with cough (protective effect in males and risk conferring in females). | [63]     |
|       |              | Erectile dysfunction              | Sildenafil                                      | 113/118      | German           | ACE I homozygous patients are better responder to sildenafil. | [64]     |
|       |              | hypertrophic cardiomyopathy (HCM) | -                                              | 368          | Dutch            | ACE-IE was significantly associated with the Wigle score. | [65]     |
|       |              | Post exercise CK increase         | -                                              | 70           | Healthy athletes | ACE II/D was associated with elevated CK activity and higher peak CK levels. | [66]     |
|       |              | Psoriasis                        | -                                              | 207/ 182     | Asian Han        | ACE II genotype was associated with higher risk of early-onset psoriasis. | [67]     |
|       |              | Cardiometabolic disease          | Chlorthalidone, calcium channel blocker (amlodipine) or ACEI (lisinopril) | 9309/ 8164   | -                | ACE I/D polymorphism was associated with fasting glucose level during antihypertensive treatment. | [68]     |
|       |              | Heart failure (HF)               | -                                              | 58           | Canadian Caucasian | AGT (T235)/ACE(D) combined polymorphisms associated with HF predisposition | [69]     |
|       |              | Pneumonia                        | -                                              | 1239/2400    | Asian Han        | ACE-DD genotype of rs4340 polymorphism is associated with increased risk of pneumonia. | [70]     |
|       |              | Multiple sclerosis (MS)           | IFN-β1a treatment                              | 391/ 380     | Persian          | Higher prevalence of ACE I allele in MS patients, overrepresentation of the I allele in unresponsive patients to IFN-β. | [71]     |
|       | rs1978124    | Hyperension                       | Anti-hypertensive (I/M %) 16.05/ 12.59         | 1099/756     | Chinese Han      | ACE I allele is associated with higher serum level of ACE. Significant haplotype: G-T-G-A-G (rs1978124, rs2106809, rs1403543, rs5194, rs56204867) rs2074192 (TT) and rs714205 (CC) were higher in DR in female (P < .05). | [72]     |
|       | (A1075G)     | Retinopathy T2DM                  | -                                              | 743 cases    | Chinese Han      | The rs1978124, rs2046863, rs2074192, rs233575, rs4240137, rs4646156, rs4646188, rs879922 were associated with T2D. The rs879922 is common maker for T2D and related cardiovascular risks. | [73]     |
|       |              | -                                 | 275/272                                        | Uygurs       | Chinese Han      | T allele of rs2106809 and C allele of rs66362777 conferred risk for HCM. | [74]     |
|       | rs2106809    | T2 Diabetes                       | -                                              | 261/ 609     | Chinese Han      | T allele confers a high risk for hypertension and reduced antihypertensive response to ACE inhibitors. | [75]     |
|       |              | Hypertension                      | ACEI Benazepril/Imidapril                      | 497          | Chinese Han      | Lower BP in CC/CT carrier female | [76]     |
|       | rs2074192    | hypertrophic cardiomyopathy       | -                                              | 265/289      | Chinese Han      | ACE (DD) and rs2106809 (TT) were associated with disease in females. T allele confers a high risk for hypertension and reduced | [77]     |
|       |              | Hypertension                      | Atensol, Hydrochlorothiazide, Captopril, or Nifedipine | 3480         | Odisha, India    | antihypertensive response to ACE inhibitors. | [78]     |
|       | rs4646176    | Blood pressure                    | High/low-sodium intervention                   | 1906 cases   | Chinese Han      | rs2106809 (T) conferred higher risk of AF in males. | [79]     |
|       |              | -                                 | 289 LVH/ 358                                  | 647 cases    | Chinese Han      | ACE2 tag SNPs rs2074192 and rs2106809 as well as major haplotypes CC and TGGT are associated with blood pressure and LVH. | [80]     |
|       | rs2285666    | Fatal CAD events                  | High/low-sodium intervention                   | 1315 cases   | Finnish, Swedish | rs1514283, rs1514282, and rs4646176 were significantly associated with SBP, DBP, or MAP responses to low and high-sodium intervention. | [81]     |
|       | (G8790A)     | T2 Diabetes with stroke           | -                                              | 1132/ 453    | Han Chinese      | G8790A is a risk factor for hypertension in Han-Chinese males, and females from other ethnicities. | [82]     |

Table 3
Association between ACE/ACE2 polymorphisms and human disorders in different populations.
3. Association between ACE/ACE2 polymorphisms and human disorders

Several potentially functional gene polymorphisms have been identified in ACE and ACE2. Associations between these polymorphisms and human disorders have been assessed in different populations. The ACE gene I/D polymorphism, 287-bp sequence insertion or deletion of DNA in intron 16 (rs4340, rs4646994), is perhaps the most studied polymorphism in this regard. Being associated with the onset and course of diabetic nephropathy [55,56], the I/D genotype is regarded as a determinant of ACE expression levels in plasma, cells, and tissues [57–59]. Moreover, the ACE2 rs2074192 and rs2106809 polymorphisms have been associated with lower levels of circulating AT-1 [1–7] [60]. Table 3 shows the results studies which assessed the association between ACE polymorphisms and human disorders.

Wigle’s score, a point score system which takes into account the thickness of the ventricular septum, hypertrophic cardiomyopathy (HCM), Blood pressure (BP), Type 2 diabetes mellitus (T2DM), diabetes thickness of the ventricular septum, hypertrophic cardiomyopathy (HCM), Lone atrial fibrillation (AF), Hypertensive left ventricular hypertrophy (LVH), Systolic/diastolic blood pressure (SBP/ DBP).

4. Associations between microRNAs (miRNAs) and ACE-related pathways

MicroRNA (miRNAs) as regulators of gene expression have been involved in several ACE-related pathways and have been shown to alter expression of ACE proteins or being altered by ACE proteins. These small-sized RNAs can bind with the 3′ untranslated region (3′ UTR) of their targets to stimulate degradation of the target mRNA and suppress translation. Moreover, miRNAs can interact with 5′ UTR, coding regions, and promoters, thus regulating gene expression by various mechanisms. Secretion of miRNAs in extracellular components provides them the ability to participate in the cell-cell communication [85]. Table 4 shows the results of studies which assessed association between miRNAs and ACE proteins.

Hypoxic pulmonary hypertension (HPH), let-7b knockout (let-7b−/−), Doxorubicin-induced heart cardiomyopathy (DHC), ALI-induced apoptosis of pulmonary endothelial cells (PECs).

5. Discussion

In the current study, we reviewed the available literature about the expression pattern of ACE peptidases and the influence of various disorders and medications on the levels of these proteins. Expression level of ACE2 has importance in severity of infection with SARS-COV-2 and the extent of lung injury [18]. Most recently, human recombinant soluble ACE2 (hrsACE2) has been shown to inhibit growth of SARS-CoV-2 and interrupt early stages of infections with this virus [91].

Based on the abundance of genetic modifying factors in determination of ACE2 levels, it is advisable to create a risk predictive panel to determine propensity for severe infection of individual. Whole genome sequencing of the patients’ samples is the best method for identification of genetic variants that determine severity of the disorder. If a few genes were recognized that have a significant impact on the variability of COVID-19 course, a genetic test for coronavirus susceptibility could be simple to make, cheap and accurate. However, much more genes could be involved in this process. Perhaps a complex regulatory pattern of genetic expression which is involved in the physiology of the lung and upper respiratory tract shape in addition to ACE2 might contribute in this disorder.

Assessment of association between ACE proteins expression and human disorders has implications in health consequences after recovery from the primary SARS-CoV-2 infection. This would be a next important issue after extinguishing of the pandemic.

| miRNA      | Disease                        | Function                                                                                       | Samples                           | Reference |
|------------|--------------------------------|-------------------------------------------------------------------------------------------------|-----------------------------------|-----------|
| let-7b     | Hypoxic pulmonary hypertension | HIF-1-dependent hypoxia is stimulated let-7b inhibited ACE2 expression via the HIF-1-to-let-7b-ACE2 axis and the let-7b-ACE2 axis. | HEK-293T cells                    | [14]      |
| let-7b     | let-7b−/− rat                  | Mouse model lung injury was alleviated by let-7b.                                               | let-7b−/− rat                     | [18]      |
| miR-421    | Cardiovascular disease (CVD)   | miR-421 down-regulate ACE2 expression.                                                            | Circulating lymphocytes           | [14]      |
| miR-1246   | Acute respiratory distress syndrome | miR-1246 up-regulate ACE2 expression. This is a reparative process in alveolar epithelial cells and may contribute to lung injury. | HEK-293T cells                    | [13]      |
| miR-483-3p | Vascular diseases              | miR-483-3p target 3′-UTRs of AGT, ACE-1, ACE-2 and AT2R.                                         | Human embryonic kidney (HEK-293)  | [13]      |
| miR-200-3p | Acute respiratory distress syndrome | miR-200-3p inhibit ACE2 expression. This is a process which leads to a protein expression that reduces the severity of ALI by inhibiting the apoptosis of PECs. | Vascular smooth muscle cells (A549) | [13]      |

Table 4 Summary of studies which assessed association between miRNAs and ACE proteins.
Hypertension is reported to be the most common comorbidity in SARS-CoV-2 infection [92], and the ACE protein is a target for ACE-inhibitors which are used in the treatment of hypertension to ultimately decrease the amount of Ang II. Some polymorphisms in ACE gene are reported to influence the efficacy of these inhibitors among them is the homozygous ACE haplotypes which lead to faster response to ramipril [61]. The expression and function of the ACE itself are affected by its polymorphisms which are associated with susceptibility to different diseases such as hypertension and diabetes mellitus [93]. Notably, polymorphisms in both ACE and ACE2 are important in the regulation of the ACE2 expression [94,95].

On the other hand, a meta-analysis has reported association between the administration of ACE inhibitors and reduction in risk of pneumonia. Notably, ACE inhibitors may be more efficient in reducing the risk of pneumonia in Asian patients. Also, treatment with ACE inhibitors was associated with a significant reduction in risk of pneumonia-related mortality compared with controls [96]. This may be related to the dual effect of ACE2 in viral infection and protection against acute respiratory distress syndrome.

Although the ACE/ACE2 regulation is complicated, it seems that in the absence of ACE the accumulation of angiotensin I may lead to the upregulation of ACE2. Whether this could facilitate the viral infection, is plausible because ACE2 is considered as a specific target for coronavirus treatment [95]. It means that the population-based differences in the ACE2 expression may affect the efficacy of a future antiviral treatment.

In brief, we summarize that coronaviruses, such as SARS-CoV and SARS-CoV-2, utilize ACE2 receptor for cell entry and infection. We know that the most severe consequence of the SARS-CoV-2 is pneumonia, which develops mostly in elderly males and subjects with comorbidities like diabetes, kidney disease, hypertension [97]. Besides, ACE2 has a protective role against acute respiratory distress syndrome. Thus, it can be concluded that decreased ACE2 level contributes to severe consequences of SARS-CoV-2 infection, while ACE2 is essential for the virus-cell fusion. One explanation for this controversy is a viral-induced translational derepression of ACE2 at the first stage of the infection [98]. However, a recent in silico analysis of sex bias severity of SARS-CoV-2 infection did not support the association between ACE2 genetic variants and disease severity/sex bias in the Italian population. Yet, TDOMNode levels and genetic variants were suggested as potential candidate modulators of the disease course [99].

Accordingly, among the top 38 eQTLs in ACE2, the strongest expression positive eQTL is more prevalent in East Asian females [100]. We also suggest epigenetic regulation by the potential miRNAs targeting on ACE2 transcripts. The results of the Targetscan database (www.targetscan.org) list miR-200c-3p and miR-429 among the most prominent miRNAs that target ACE2. Up-regulation of miR-200c-3p is induced by a viral infection which leads to the downregulation of ACE2 [13]. Also, miR-421 is proved to downregulate ACE2 translation [14].

Interestingly, we have analyzed the well-studied I/D in ACE in Iranian patients with multiple sclerosis and reported association between this polymorphism and response to Interferon-β treatment [71]. Thus, ACE/ACE2 polymorphisms not only can predispose individuals to diverse diseases, but also they can modulate response of patients to therapeutic options. Both activities have implications on the susceptibility to SARS-CoV-2 infection and the disease course. Another research area might be the identification of the difference between ACE/ACE2 expression levels and their regulating factors, such as the mentioned eQTL and miRNAs, between patients with severe and mild symptoms in different ethnic groups to find the possible effect of ethnicity, gender and the period of the disease on the ACE/ACE2 expression.

In addition to the routine models for investigating of the pathological events during infections, tissue engineering methods particularly “advanced biomaterials” or “functionalized scaffolds” [101] would provide study models to investigate the potential of such approaches in the treatment of the disorder. As an advance in the field of functional studies, the obtained results from “safe” in-vitro models which work without any additive can be applied in human models [102].

Taken together, the data presented above show the diversity of factors that modulate ACE/ACE expression both in physiological conditions and in the course of SARS-CoV-2 infection. Different levels of expression and function of the ACE proteins, underlying disorders such as diabetes and hypertension, administration of certain medications, especially ACE inhibitors and calcitriol, and the existence of certain genomic variants within ACE genes that modulate function or expression of the encoded proteins are possible explanations for the observed difference in the response of individuals to the SARS-CoV-2 infection. Exploration of the role of these factors can lead to design of appropriate therapeutic modalities based on the personalized risks. Such personalized approach is expected to be more effective. Exploitation of the next generation sequencing methods at both genomic and transcriptomic levels would be a practical strategy in this regard.

In conclusion, the observed differences in the course of SARS-CoV-2 infection can be attributed to several genetic factors, comorbidities and administration of medical regimens that modulate expression of ACE proteins.

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