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Review Article

Risk of increased expression of ACE2 membrane protein in patients with hypertension: Review of COVID-19

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Abstract

Context: In late 2019, COVID-19 launched a pandemic from around Wuhan, China. It`s called the SARS-CoV-2 virus which belongs to the corona family and it has a lot in common with SARS-CoV-2, but it has been reported to be more common.

Evidence Acquisition: The risk of the virus is high for people with high blood pressure and use medication. The reason for this potential and risk for COVID-19 is an increase in expression in a membrane protein called ACE2. This protein is responsible for converting Ang I to Ang1-9 as well as converting Ang II to Ang1-7.

Results: Its pathogenic role is due to its receptor for SARS-CoV-2 and SARS-CoV. Research has shown that there is a significant link between hypertension, Increase the expression and activity of ACE2 and having coronavirus. That`s why our goal is to remind people of high blood pressure about the risk of developing Covid-19. We studied ACE2 and Covid-19 from a clinical and biological point of view. In the following we have shown the position and the type of virus connection to ACE2 with the help of protein database.

Conclusion: In the SARS-Cov-2, there are four structural proteins and several non-structural proteins together with capsid can contain positive-stranded RNA viruses. Studies have shown that the Spike (S) protein binds strongly to the chain E and F with the ACE2 receptor.

Keywords: COVID-19, SARS-CoV-2, ACE2, Hypertension, Receptor

1. Context

COVID-19 is a global challenge that has become an unprecedented pandemic. Suddenly, the virus spread to all parts of Wuhan, China, Asia, conversely the rest of the world, consequently the epidemic of the new virus soon becomes a global pandemic. COVID-19 is also known as SARS-CoV-2, moreover World Health Organization (WHO) has also named the new virus 2019-nCoV. The new virus has infected about 2 million people worldwide with respiratory and heart problems. The new Coronavirus is spread faster than its two older families. The new one (SARS) is the cause of acute respiratory syndrome and the second one (MERS) is the cause of the Middle East respiratory syndrome. However, to date, fewer deaths have been reported. However, more than 200000 people in different parts of the world have died. More than 200 countries have been affected by the new corona virus, nevertheless no definitive treatment or confirmation has been reported [1-5].

For coronavirus, a new virus has been reported from people without clinical symptoms, with mild clinical symptoms and acute clinical symptoms. It is important to note that in all three cases, they're

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individuals retained the potential to be transferred to another person [6]. Another important issue is the two-week-long incubation period of the virus, which makes it difficult to diagnose quickly. The solution proposed today is home quarantine in this pandemic, which in itself has many difficulties, including the difficulty of controlling economic, social and psychological problems in society. Every one of different ages is more likely to be infected with the new corona virus, but with significant differences, people over the age of 60 are more likely to be infected. Patients with a history of immunodeficiency (such as cancer patients undergoing chemotherapy, people with organ transplants, MS patients and people living with HIV) [1, 2] and another group of people with underlying diseases, such as diabetics [3], heart and vascular patients [4], as well as people with high blood pressure, are more likely develop acute respiratory syndrome. Reports indicate that these people are in greater need of hospitalization. Significantly, patients need more ICU care and need longer treatment. The researchers found that most deaths were in people with a previous history of the disease [5].

Research has shown that ACE2 receptor binds to COVID-19 in the host cell. The ACE2 has previously been reported as a receptor for SARS-CoV and MERS-CoV. According to the studies on SAR-CoV the cause of further complications in the respiratory and cardiac systems in the face of this virus was reported to be an increase in the expression of ACE2 in heart and lung patients. It should be noted that people with primary hypertension and secondary hypertension have a similar position to heart and lung problems [6-9].

In this study, we will review the clinical and biological characteristics of COVID-19 and ACE2. The goal is to warn patients with high blood pressure, which will increase the potential for conflict with COVID-19 to the increased expression of ACE2 in this group of patients. We also reviewed the protein structure and the type of virus binding to the receptor, used protein database (www.pdb.org).

2. Evidence Acquisition

2.1. Hypertension

Hypertension is a chronic high blood pressure that is considered a silent killer. High blood pressure is usually asymptomatic, consequently it is difficult to diagnose and treat. Late diagnosis leads to a large number of people with high blood pressure today who needs medication to control their blood pressure. Countless people around the world will have more potential for COVID-19 which we will discuss below [10, 11].

In a brief review, we note that the heart rate is effective in high blood pressure and causes the blood to move forward and toward the flexible walls of the arteries. During each stroke, the heart muscle is at rest and then the arterial walls return to their original position. In this way, the blood can move to the tissues of the body. In people with hypertension, the pressure inside the arteries is so high that at least some of the blood vessels are destroyed. In general, patients with high blood pressure are divided into two categories: Primary hypertension, and secondary hypertension [12, 13].

Factors that play role in primary hypertension include age, gender, obesity, high cholesterol and triglycerides, have also caused of secondary hypertension include kidney problems, aortic valve stenosis, endocrine disorders, long term use of birth control pills, excessive salt intake, smoking and alcohol [4, 15].

Accordingly, If we accept that hypertension will increase the risk of developing SARS-CoV-2 the above factors can indirectly affect the risk of COVID-19.

2.2. Drugs affecting Angiotensin (Ang)

Two groups of target drugs are used for this study in hypertension patients:

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1) Angiotensin-Converting Enzyme (ACE) inhibitors that can reduce Ang II (a substance that constricts and dilates blood vessels), as a result your arteries will relax and your blood pressure will drop, improving your heart function.

2) Angiotensin II Receptor Blockers (ARB) inhibitors that block angiotensin instead of reducing angiotensin levels [16, 17].

Table 1: Two groups of drugs that affect Angiotensin (www.mayoclinic.or**g)**

Examples of angiotensin II receptor blockers include:	**Examples of ACE inhibitors include:**
• Azilsartan (Edarbi),	• Benazepril
• Candesartan (Atacand),	• Captopril.
• Eprosartan Irbesartan (Avapro),	• Enalapril
• Losartan (Cozaar),	• Fosinopril.
• Olmesartan (Benicar),	• Lisinopril
• Telmisartan (Micardis),	• Moexipril.
• Valsartan (Diovan	• Perindopril.
	• Quinapril

Mayo Clinic; www.mayoclinic.org

2.3. Structure ACE2

ACE2 is Mono-Carboxylic peptides and is one of the membrane proteins encoded by the ACE2 gene on the chromosome. This gene is made up 18 Exones which are very similar to the Exones of the ACE gene. Therefore, the synonym of acetic acid is very similar to ACE. Both of these enzymes are considered to be extracellular proteins that have catalytic properties [18,19]. ACE2 consisting of 814 amino acids consisting of six chains of A, B, C, D, E and F (Figure 1). Also, ACE2 have seven domains: First domain of 114 amino acids is involved, accordingly, is most similar to ACE (chain A), which is similar to 6-84 amino acids. The second domain consists of two parts, which is between 115-139 and 183-222 amino acid. Third domain consists of 140-182 amino acids. Forth and fifth domains consist of two parts respectively 242-263 and 512-616 amino acids for forth domain and 264-288 and 437-511 for fifth domain. Sixth domain consists of 313-436 amino acids and seventh domain consist of 617-742. ACE2 has 17 amino acid in its terminal, which are integral and signaling sequence for ACE2. Near the end of C terminal, there is 22 amino acid with hydrophobic properties, moreover are the transmembrane sequences of this protein. Also, C terminal consists of a cytoplasmic domain, compound containing 43 amino acids, moreover is a place for phosphorylation [20, 21].

These three domains are not similar for ACE2 to ACE, in fact, there are similar similarities between 220 amino acids. This is similar to glycoprotein domain for transmembrane. Many of the functions of the different domains of ACE2 still remain unknown. The most similarities to zinc-binding motif have been identified in both ACE2 and ACE1 proteins. In total, ACE2 has eight amino acid cysteine, which has the potential to form four disulfide bonds. Six of these cysteines are at the end of the N and C domain. Another feature of this receptor is the presence of seven glycosylation sites [18, 22].

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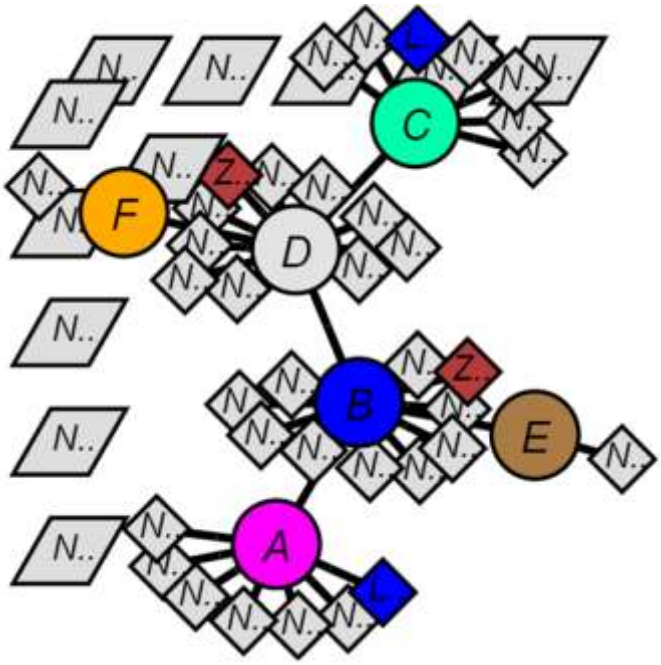

Figure 1. Six chains defined for ACE2, importance of the chain E and F in the position of the connectin for Covid19. N: N-Acetyl- D- Glucose Amino; Z: Zinc Ion; L: Lysine.

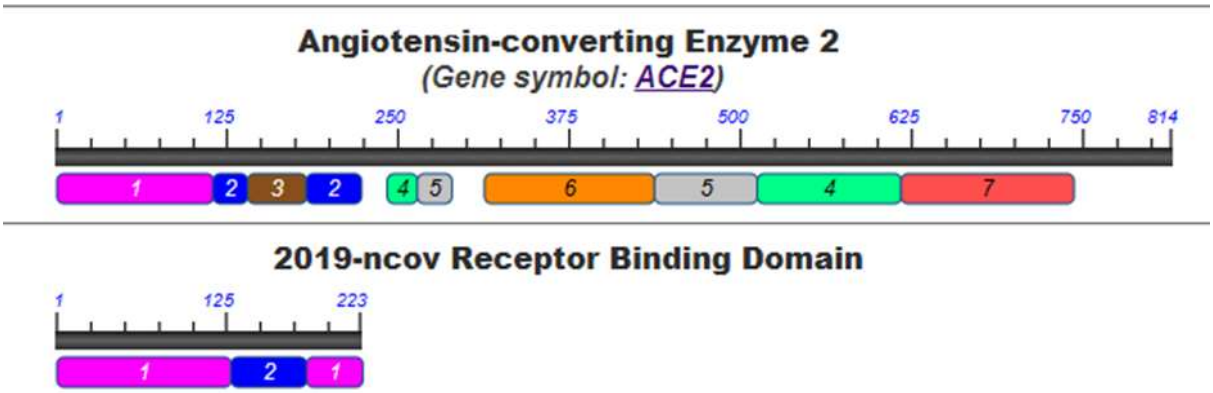

Figure 2. Seven Domain defined for ACE2, based on the division of the amino acid sequence classification are also the three parts connected to the receptor for Covid19 which is two Domain. The domain is two parts and includes more amino acids. In total it has 223 residue.

Briefly, the depends on the Renin Angiotensin System (RAS) for ACE. Accordingly, RAS is a converter for converting Ang I to Ang II with the help of ACE. ACE2 plays a key role in converting AngI to Ang1-9 as well as converting Ang II to Ang1-7. (Ang II + H2O <=> Ang1-7 + L-phenylalanine). Also Ang1-9 can convert to Ang1-7 by ACE. As a result, these affect ACE2 through Ang1-7 and masR6 on the vasodilatory and anti-fibrotic actions [23, 24]. It is briefly shown in figure 3.

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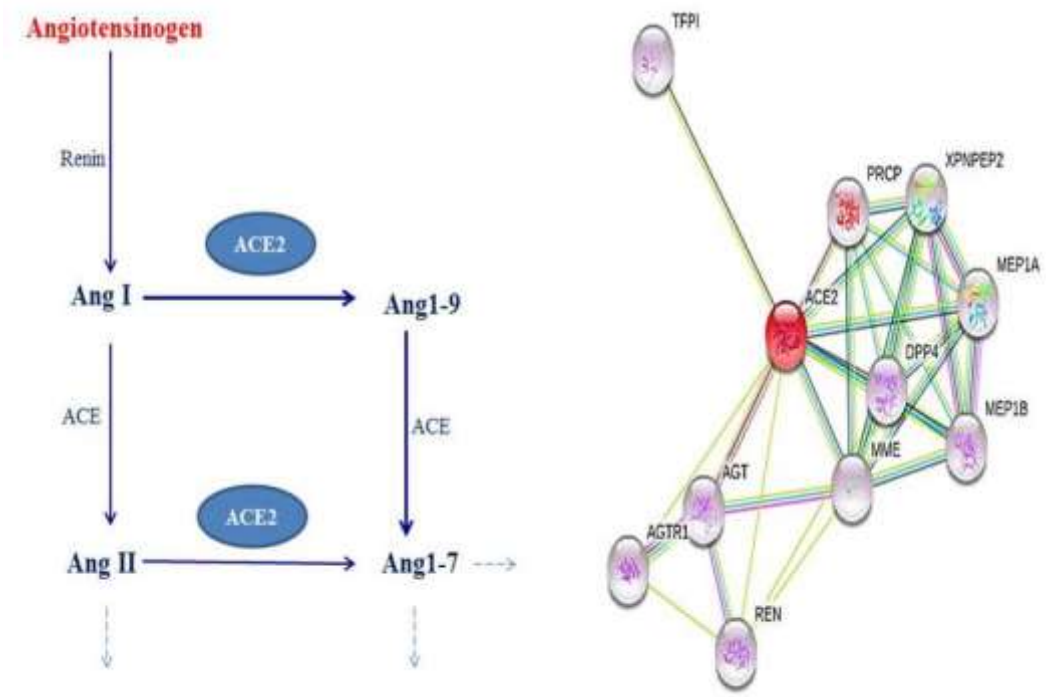

Figure 3. ACE2 position performance stand for Angiotensinogen, and Protein-Protein Interactions.

3. Results

Clinical COVID-19

Origin: there are various reports about the original origin of this new coronavirus, but what has been identified is that it was first spend by seafood market workers in Wuhan, China. It is likely to lead to the transfer of semi, cooked seafood to humans. Some reports of bat-to-human transmission are primary origin. Moreover, given these two possibilities the possibility of genetic manipulation and biological attack has not yet ruled out, nevertheless the percentage is very low, and is no evidence [25, 26].

Epidemiology: COVID-19 started with a high prevalence epidemic in Wuhan, China, on 29 December 2019, consequently become a worldwide pandemic that spread to all countries [24].

To date, there is no known limiting factor for new coronavirus. Human-to-human transmission is happening. The most likely transmission is through direct contact with carriers, although transmission from the infected surface of the virus is also possible. A significant portion of the spread has been related to human-to-human transmission within the family, friends and working communities, as well as reports on medical stuff notifications. What is clear is that the travel and movement of carriers with symptoms and without symptoms has contributed to the rapid spread of the new coronavirus [27, 28].

Genetic studies of SARS-CoV-2 have shown that the new virus has two types, S and L. L type is the ancestral version and has less prevalence, conversely more invasion and faster than S type. At the beginning of the prevalence of COVID-19, L type was predominant but the weakened S type was more prevalence [29, 30]. It should be noted that in some countries such as Italy, Spain, France and Iran more deaths were reported than China. Due to the fact that the five of onset of the outbreak, the peak of the pandemic, the amount and quality of the population in different geographical areas are different also different reports have been sent. Also, due to the non-completion of this pandemic. It is not possible yet to report for the death rate of COVID-19 [27, 31, 32].

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Clinical signs: People with COVID-19 have been reported to have no primary clinical symptoms, may mild clinical symptoms similar to the common cold, or people with acute clinical symptoms including respiratory problems. Dry cough and fever (T>37.8) are the most prominent features of the new coronavirus. It has been reported that these symptoms will not go away after 5 days and are progressive. Noninfectious sore throats have also been reported rarely. In acute conditions, drug resistant, decreased levels of consciousness and hypercapnia hemodynamics instability occur [33-35].

Diagnosis: The findings show that people with COVID-19 have a positive C-reactive protein (CRP) and will usually be more than 100. According to lymphopenia the first recommended tests for these people are CBC and CRP. It is also important to check the Oxygen saturation (SpO2) of the blood pressure [36, 37]. These laboratory tests are recommended for all people with or without clinical symptoms. Moreover, the CXR/CT scan is essential for all people who are at higher risk or have respiratory [38]. Figure 3 shows the proposed diagnostic action model. Vital signs and laboratory findings that can be used to diagnose patients with COVID-19 includes:

- Rspiratory Rate > 24
- SpO2 < 90 on ambient air
- Heart Rate >125 beats/min
- C-Reactive Protein (CRP) >100
- D-Dimer>10000 ng/ml
- Progressive Lymphopenia
- Creatine Phosphokinase (CPK) > twice upper limit of normal
- Elevated Troponin I
- High Ferritin >300 ug/l
- Elevated LDH

In addition to the CT scan the definitive diagnosis of COVID-19 is made by testing the new coronavirus molecular with RT-PCR clinical samples for this molecular test of the upper respiratory tract include two nasopharyngeal swabs, also recommended for patients with lower respiratory tract sampling include endotracheal aspirin and Broncho alveolar lavage [38, 39].

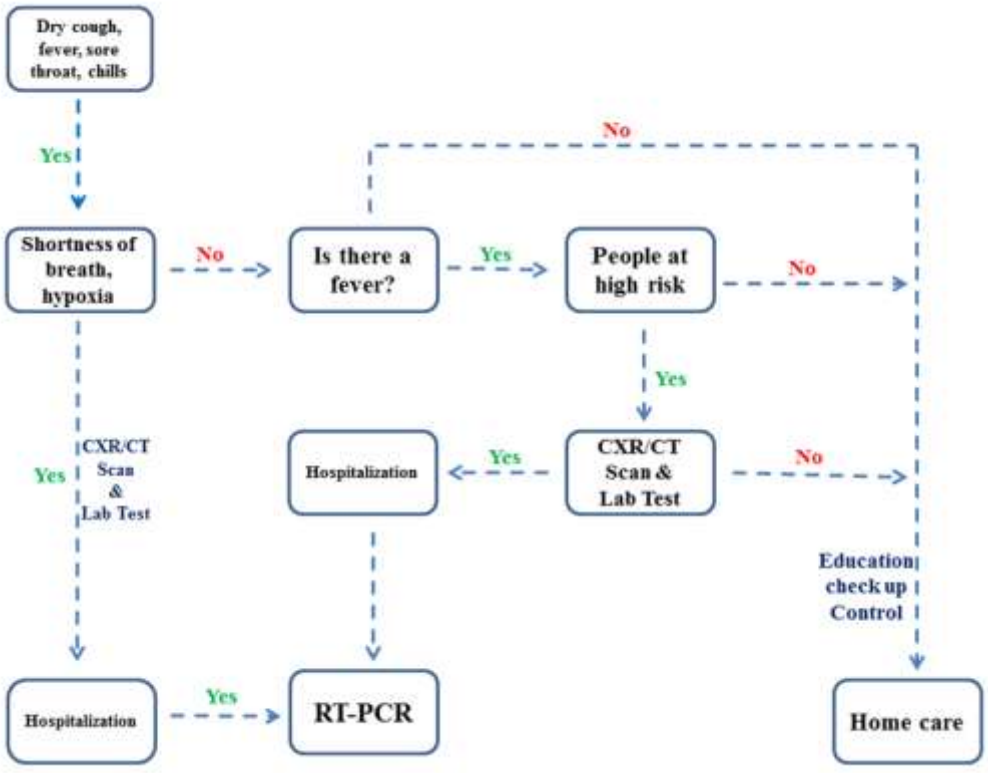

Figure 4. Para clinical diagnosis pattern for COVID-19

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Treatment: no definitive treatment or preventive vaccine has been reported for COVID-19 (2020, Apr 20). As a result, the treatment offered to date is limited to supportive therapies, including oxygen and increasing immunoglobulin G part of the treatment is under the influence of antiviral drugs and Corticosteroid. Antiviral drugs have been suggested in cases like HIV, MERS-CoV and SARS-CoV. The recommended drug regimen in Iran for people with COVID-19 is the use of Hydroxyl-Chloroquine or Chloroquine-Phosphate. Moreover, complementary drugs include Lopinavir or Ritonavir and Atazanavir or Ritonavir. The American food and drug administration and WHO have emphasized the use of Hydroxyl-Chloroquine [40-42].

Biological COVID-19

Classification: The coronavirus family divides the virus into two subfamilies includes: *coronaviridea* and *letrovirinea*. In the coronavirus family, the virus includes four general that cause *Alpha-Coronavirus* and *Beta-Coronavirus* infections in humans, but *Gamma-Coronavirus* and *Delta-Coronavirus* in birds are pathogenic [40]. The full classification is shown in figure 2 of Hoffmann et al`s paper (2020) [8].

Structure (Genome and protein): COVID-19 is an RNA virus (enveloped and positive-stranded RNA virus) with a lipid coating that is supported by several proteins[22]. RNA length in SARS-CoV-2 is 29.9 kb but for SARS-CoV is 27.9 kb and for MERS-CoV is 30.1 kb[25]. The SARS-CoV-2 genome has 14 ORF, encoding a total of 27 proteins. Two types of structural and non-structural proteins are known for COVID-19. The structural protein such as glycoprotein called Spike (S), type of coating protein called small Envelope (E), Matrix (M), Nucleocapsid (N), which is encoded at the end of three genomes [38, 43] . The end of 5 genome of polyprotein pp1a and pp1a/b are encoded by ORF1a and ORF 1ab genes. These genes are also involved in encoding nonstructural proteins like snp7-nsp10 and snp12-snp16. They encode a total of 16 non-structural proteins. For COVID-19 eight nonstructural proteins are also known to be encoded by genes in region 3 of the genome (3a, 3b, p6, 7a, 7b, 8b, 9b and orfl4). Accordingly, some of the non-structural protein like 8a, 8b and 3b the difference between SARS-CoV-2 with SARS-CoV [44].

S protein us a hemotrimer that has more 1200 amino acids per monomer. This protein is highly glycosylated and uses the peptide sequence sign at the end to reach the endoplasmic reticulum. This protein is responsible for binding to the ACE2 receptor (figure 5). In addition to S protein, there is a hemagglutinin- esterase (HE) dimmer protein in the Beta-coronavirus that binds to glycoprotein ACE2 on the host cell surface via silicic acid. This protein is involved in the proliferation and spread of the virus [43, 45].

N protein is attached to the ring genome and is highly phosphorylated. The shape of the rosary like of this protein, helps Replicase-Transcriptase Complex (RTC) and the encapsulation of the genome. These are possible functions of this protein [41, 46].

The lowest amount of structural protein is related to E protein. The role of this protein in ion transport is to influence the process of virus assembly and facilitate virus release. Protein is actually referred to as a possible ion channel in the virus. What is clear is that the role of this virus in the pathogenesis process is more important than reproduction process [4, 47].

The most abundant structural protein in the new coronavirus is related to M protein, that is member protein, a dimmer and can have different structures. This protein binds to the nucleocapsid [21, 48].

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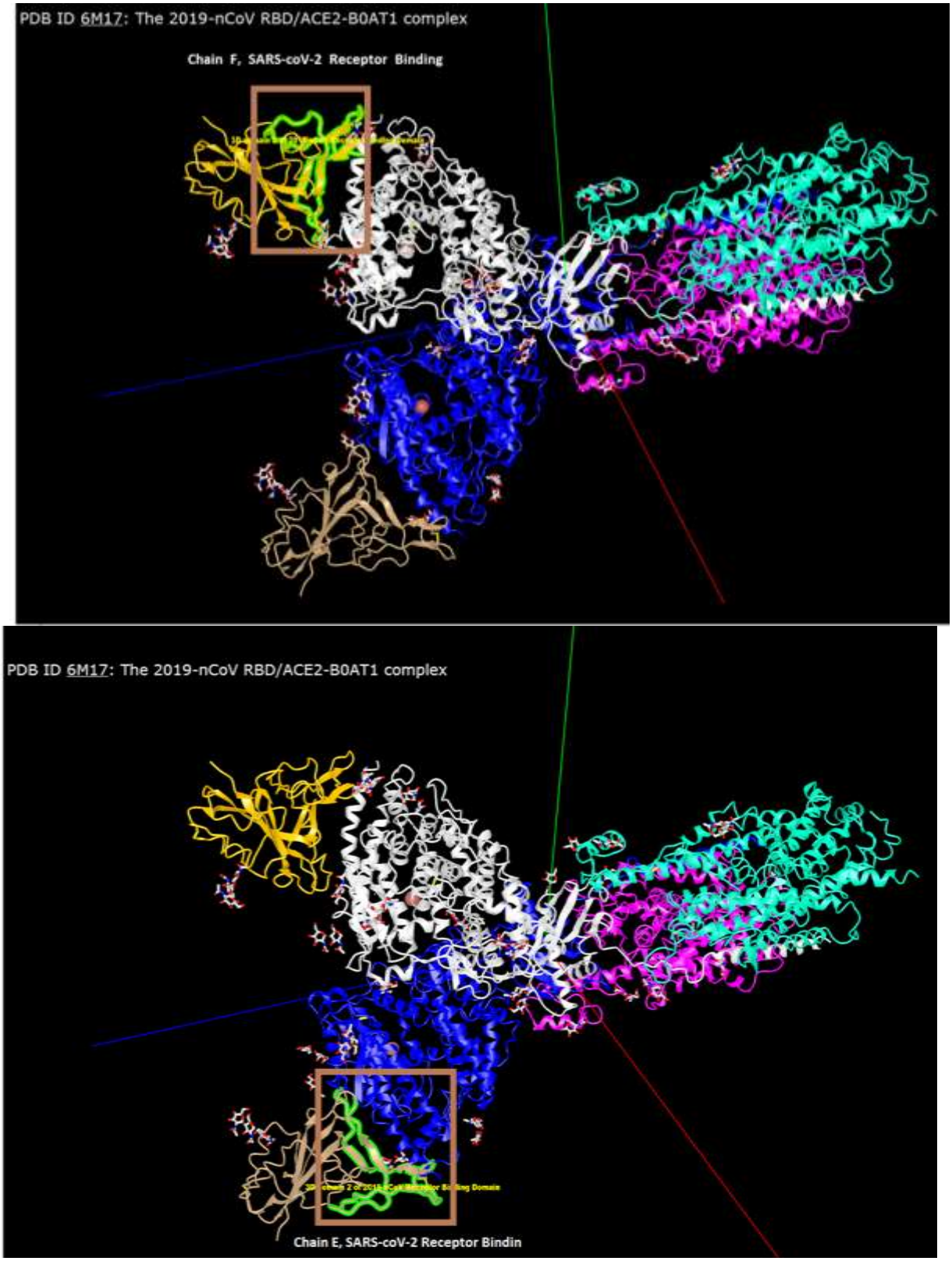

Figure 5. The green highlight section is related to**: A)** Chain E, SARS-CoV-2 Receptor Binding Domain; **B)** Chain F, SARS-CoV-2 Receptor Binding Domain, [Used protein database (www.pdb.org)].

The association of ACE2 with hypertension

Previous research has shown that the rate of ACE2 expression in hypertension increases due to the use of inhibitory drugs

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like ACE and ARB. In general, ACE2 reduces inflammation and has always been considered as a suitable and high potential target for the treatment and control of blood pressure, diabetes, and pneumonia. The link between the increase of ACE2 expression and hypertension has been examined in previous studies [19, 49]. Also, we refer you to study of table 2 in Pates with his colleagues in 2014 [19].

Long term use of effective drugs in RAS has increased the expression of ACE2, consequently due to the receptor properties of this protein, some viruses such as SARS will be the cause of viral infections. This effect is accompanied by an increase in expression and an increase in activity. The pathogenic role of this protein has been established and proven to be true for chronic hypertension as well as for blood balance. It plays a more supportive role in primary hypertension with a genetic background ACE2. So it should be said that ACE2 increases the expression of this deficiency, but does not change its activity level [50]. However Xia and his colleagues (2009) reported transgenic front of increased activity of non transgenic [51]. This discrepancy can be examined due to different types. In recent years, the average blood pressure has been rising, so the number of secondary hypertension has become critical. This failure threatens millions of people around the world. No adjustment of ACE2 has been reported for secondary hypertension [52].

Research has shown that in this type of hypertension, along with increasing expression and activity, we will have an increase in ACE2 and this is directly related to the time and dosage of blood pressure control drugs. All in all, ACE/ACE2 balance is a center for controlling and regulating blood pressure, as a result raises blood pressure by upsetting the expression [53, 54].

Relationship between ACE2 and COVID-19

ACE2 is the only known receptor for SARS-CoV-2 and SARS-CoV in the study [55]. Accordingly, Zhao et al. found that SARS-CoV-2 used ACE2 to enter the cell [56]. Specifically, the SARS-CoV-2 binds to the second domain of ACE2 via the S protein (figure 6). This second domain is in E and F chains which contains 223 amino acids (figure 7). This bond is a strong chemical that is made directly. In this connection there is a disulfide bond between the cyc_{162}-cyc_{170}. Residues involved in the binding of S protein to chain E and F, hence are shown in figure 5. Research by Van et al. Showed that the $glutamine_{394}$ binds to the $lysine_{31}$ have a critical point. Earlier it was revealed that residues close to $lysinee_{31}$, $tyrosine_{41}$, and residues (82-84 and 357-353) in human ACE2, accordingly are important for S protein binding in coronavirus. The more connection, the more cells become infected and this helps the cell cycle [57, 58].

From another point of view, the strong binding between S protein and ACE2 interferes with the function of ACE2. As mentioned earlier, ACE2 plays an important role in controlling blood pressure and heart beat.

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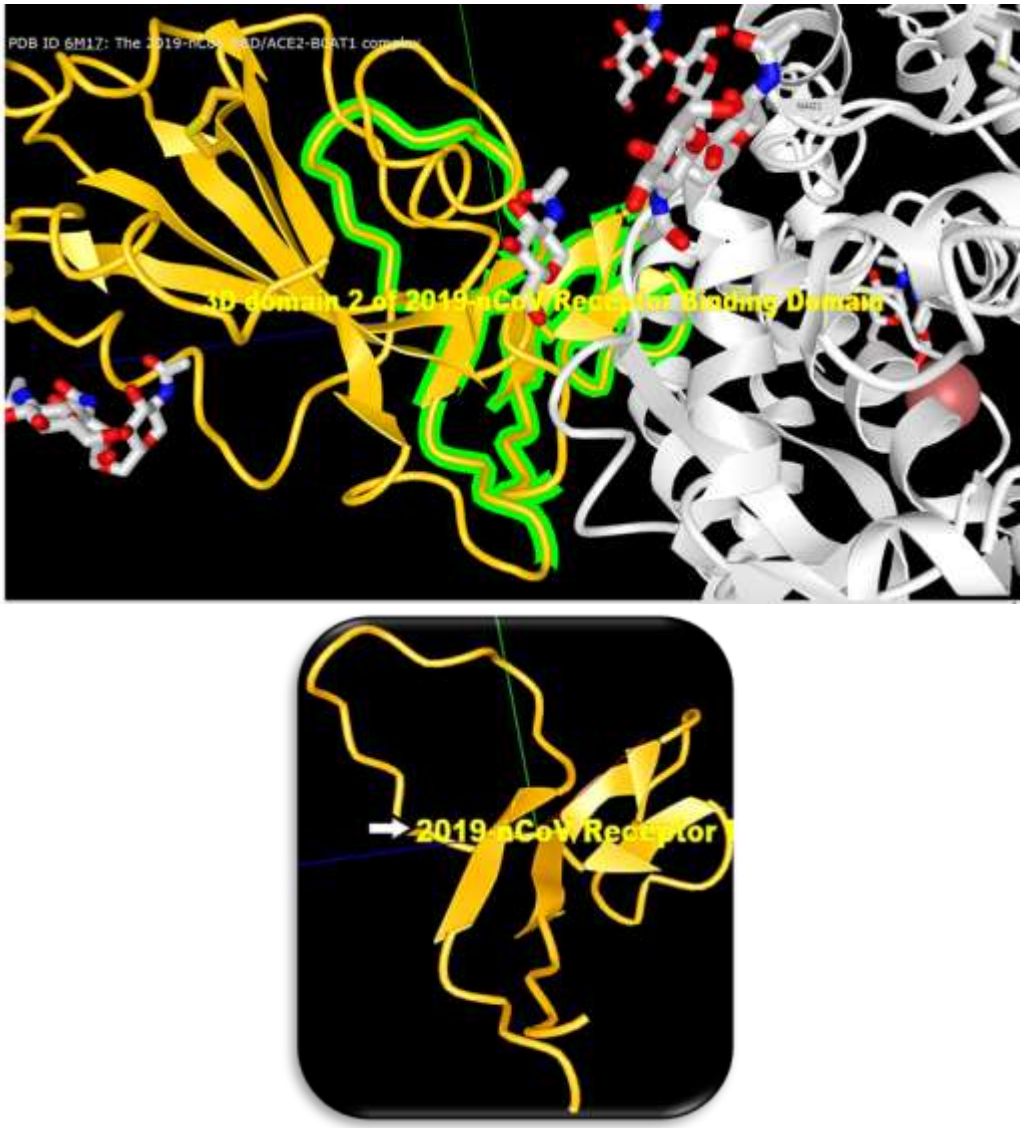

Figure 6. Domain connector, [Used protein database (www.pdb.org)]

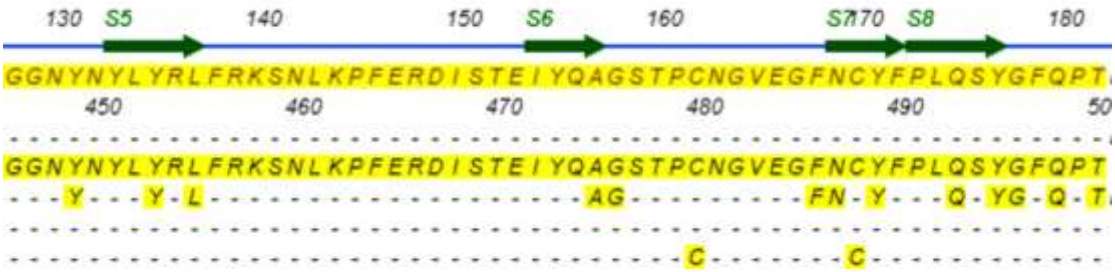

Figure 7. The amino acids involved in the binding of the S protein with E and F chain ACE2 receptor for SARS-CoV-2

4. Conclusion

High ACE2 expression in hypertension patients greatly contributes to the life cycle, cellular assembly and genome proliferation of COVID-19. Consequently, it seems that monitoring of these patients is necessary to prevent to COVID-19. Depending on the patient`s condition and if possible, a medication regimen should be used that has the least effect on increasing the expression and ACE2 activity.

During a pandemic and after a pandemic, the most important thing is to lower and control your blood pressure naturally or

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with new medications. Controlling blood pressure is directly related to a person`s lifestyle so lifestyle changes can reduce the need for high blood pressure medications. We recommended that more research be done on drugs that affect ACE/ACE2 balance, ARB drugs, ACE2 expression and activity. Moreover the use of nanoparticles based on green chemistry can be a good solution.

Conflict of Interest

The authors declare no conflict of interest.

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