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Clinical Investigation and In Silico Analysis of ACE2-Mediated Electrolyte Imbalance in Post-COVID-19 Recovery Patients

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Abstract

Angiotensin-converting enzyme 2 (ACE2) receptors play a pivotal role in regulating blood pressure and electrolyte homeostasis. SARS-CoV-2 exploits these receptors to enter host cells, potentially disrupting their physiological role and leading to electrolyte imbalances in recovered patients. The objectives of this research is to investigate the prevalence of persistent electrolyte disturbances in individuals recovering from COVID-19 and to use in silico modeling to examine the molecular interaction between the ACE2 receptor and the viral peplomer protein. A total of 200 recovered COVID-19 recovered patients (aged 20–49 years) and 100 healthy controls (aged 22–46 years) were evaluated. Serum levels of calcium, potassium, sodium, and chloride were measured in the study subjects in addition to urea and creatinine in order to assess the kidney function of the subjects. Computational docking and structural analysis were performed using CASTpFold to analyze the active site of the human ACE-2 receptor (PDB: 1R42) and its interaction with the SARS-CoV-2 spike protein. Recovered individuals exhibited high rates of hyponatremia (52.5%), hypokalemia (47.5%), and hypocalcemia (62.5%), with lower incidences of hypochloremia (5%), hypernatremia (4%), and hyperchloremia (7.5%). In silico analysis revealed a large ACE2 active site (area: 4183.429 Å^2; volume: 8098.169 Å^3) with clearly defined ligand-binding regions implicated in spike protein binding, providing structural insight into the receptor's functional disruption. The findings suggest that SARS-CoV-2-induced modulation of ACE2 contributes to lasting electrolyte imbalances in post-COVID-19 recovered patients. These disturbances may underlie long-COVID symptoms, highlighting the need for continuous electrolyte monitoring and potential therapeutic interventions targeting ACE2-related pathways.

Keywords: COVID-19, Electrolytes, Hyponatremia, Hypokalemia, Hypocalcemia, In silico

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the cause of the highly contagious disease known as coronavirus disease 2019 (COVID-19), which was first identified in Wuhan, Hubei Province, China. It then quickly spread to other cities within China and to other countries [1]. The

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World Health Organization (WHO), on January 30, 2020, announced this ongoing epidemic as a worldwide public health emergency, and on February 28, 2020, it increased the risk of COVID-19 to extremely high globally [2]. Fever, dry cough, weariness, muscular pains, and other signs like shortness of breath, indigestion, headache, and diarrhea are among the most typical COVID-19 symptoms [3-6]. Multiple organ systems, consisting of the digestive, cardiac, and urogenital systems, have shown evidence of SARS-CoV-2 attack [7-9]. SARS-CoV-2 activates the viral S protein to facilitate entry into the host cell by manipulating the host's receptor, ACE-2, and a serine protease, TMPRSS2. [10–12]. The identified receptor for the SARS-CoV-2 viral spike (peplomer) complex is ACE2 [17]. The gastrointestinal, respiratory, and urinary, systems all have this receptor. By tying up with these receptors, the virus can cause a range of clinical symptoms or problems [13]. After the virus binds to the ACE2 receptor, the imbalance of electrolytes may play a role in metabolic issues, which may eventually result in immunological disorders [14]. Even though the majority of COVID-19 patients fully recover without any complications, many patients may continue to experience COVID-19 symptoms after their illness has cleared up, and some may even acquire new symptoms [15]. Post-COVID syndrome (PCS) is the collective term used to describe this clinical spectrum that follows an acute infection [16]. According to some authors, PCS is the existence of signs and symptoms following an acute COVID-19 infection over some time longer than 4 weeks [17,18]. Fatigue, headaches, attention deficit, hair loss, dyspnea, myalgia, cardiac arrhythmias, and arthralgia are some of the symptoms of PCS that are most frequently described [19]. It is not surprising that COVID-19 can cause acute renal impairment. As previously mentioned, coronavirus attaches to ACE2 receptors to enter the cell. The presence of such a high concentration of these receptors in kidney cells renders the organs vulnerable to coronavirus invasion. The fluid imbalance brought on by fever or patients' decreased fluid intake is the likely factor underlying renal impairment in COVID-19 instances [20]. Supervision renal function therefore plays a crucial part in lowering mortality and preventing serious complications in COVID-19 patients. The abnormalities of electrolytes, notably hyperkalemia, are the predominant renal outcome observed in hospitalized patients with COVID-19, in accord with a collection of the latest studies [21].

The expression of ACE2s is greater in the kidneys compared to the lungs, therefore SARS-CoV-2 has a high affinity for the kidneys. SARS-CoV-2-infected pneumonia patients had lower serum salt levels than healthy individuals [22]. A severe and aggressive COVID-19 infection may be more likely to occur if sodium levels are low [23,24]. Patients with COVID-19 occasionally display dyselectrolytemia, such as hyponatremia. This electrolytic problem is frequently brought on by a range of reasons [25,26]. The most prevalent electrolyte problem found in clinical practice is hyponatremia, which has a higher mortality risk [27]. Several of the symptoms of SARS-CoV2 disease, such as muscular palpitations, heart irregular rhythms, weaknesses, and inadequate diabetes management, are shared by hypokalemia, which is commonly acquaint as <3.5 mmol/L in plasma [28,29]. Hypokalemia during SARS-CoV2 infection is principally brought on by increased aldosterone, which encourages potassium excretion in urine [30]. Hypokalemia and the imbalance of electrolyte were linked to severity of the disease [31]. Research revealed that despite only 54% of patients had inadequate potassium levels, the critically sick individuals were more likely to have hypokalemia 85% of them [30] and another study discovered that around the time of admission hypokalemia was linked to the need for invasive mechanical ventilation [32].

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Ionized calcium levels were found to be considerably lower in patients who tested positive for SARS-CoV-2 than in patients who tested negative in a recent study that gathered information from venous blood gas analysis of patients with respiratory illnesses [33]. In addition, two retrospective case-control investigations indicated that COVID-19 patients had lower total calcium levels than outpatient controls who were age- and sex-matched population-based controls [34 – 36].

The imbalances of electrolytes commonly lead to irregular heartbeat, tiredness, dizziness, confusion, blood pressure changes, twitching or muscle weakness, numbness, and seizures, among other symptoms. Patients with mild hypokalemia, for instance, are typically asymptomatic, but symptoms may appear when potassium levels are below 3 mmol/L. Weakness in the muscles, constipation, and ileus are possible symptoms. Rhabdomyolysis, arrhythmias, and even cardiac or respiratory arrest have been described with severe hypokalemia [37–39]. Clinical symptoms of electrolytes imbalance are reflections of multiple interactions of electrolytes and regulatory systems in the organism [40]. Many of the clinical symptoms of electrolytes imbalance are seen in recovered COVID-19 patients, many of which may persist even after months of recovery. Accordingly, this study uniquely integrates clinical investigation with computational analysis. Our primary clinical aim is to determine if electrolyte imbalances persist as a long-term sequela of COVID-19, potentially explaining some of its persistent symptoms. Concurrently, our computational work seeks to elucidate the molecular interactions between the SARS-CoV2 spike (peplomer) protein and the ACE2 receptor, providing a mechanistic underpinning for any observed clinical disturbances. By combining these approaches, this research aims to contribute not only to identifying a potential physiological basis for long COVID but also to offer insights that could guide physicians in monitoring and developing targeted interventions for these imbalances and their associated clinical symptoms.

Materials and Methods

Study subjects

Two groups of 300 participants were subjected to the present study; the first group include 200 COVID-19 recovered patients with age range 20-49 years as a patients group. While the second group include 100 apparently healthy individuals with age range 22-46 years as a control group who were attended to the private medical laboratories. The blood samples were collected after approximately two months from full recovery. All the participants of current study were showed negative results for the SARS-CoV2 by used RT-qPCR test. The College of Biotechnology’s scientific committee of Al-Nahrain University gave its approval to this study.

Exclusion Criteria

For the purpose of removing cases that might have an impact on the study's findings, the patients with the following criteria were excluded: patients with active (Positive) SARS-CoV2 infection, any known inflammatory condition, using diuretics, kidney diseases, diabetes and/or hypertension, recovering from recent surgeries and any tumors or cancers, using a structured questioner form.

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Collection of blood samples:

Each patient and healthy control had their veins punctured to get five milliliters of venous blood. Disposable plastic syringes were used for this procedure. The clotting process was started by transferring the blood into a gel tube and letting it sit at room temperature for 15 to 30 minutes. To separate the serum, the sample was centrifuged at 4000 xg for 15 minutes. The collected sera were analyzed immediately.

Measurement of serum electrolytes

Serum level of sodium, urea, potassium, calcium, chloride and creatinine were assessed in the sera of recovered subjects and controls using the (Cobas C311, S.N; 1230-11) automated analyzer provided with kits manufactured by Roche Diagnostics.

Statistical Analyses:

Biochemical data were analyzed using SPSS, the statistical package for social sciences, version 25.

In silico analysis

ACE2 receptors and SARS-CoV spike glycoprotein (S protein) structure analysis

The protein data bank (https://www.rcsb.org/) is an atlas for proteins that provides the 3D structure model of ACE2 protein (PDB ID: 1R42) and SARS-CoV spike glycoprotein (PDB ID: 6VXX) obtained by experiment and analysis of different information about proteins [41].

Visualization of the 3D structure of ACE2 receptors and SARS-CoV spike glycoprotein (S protein)

The PyMOL V.3.1(https://pymol.org/) is powerful and flexible interface software widely used in the visualization of 3D molecular structures of proteins, including ACE2 and S protein structures [42].

Detected the active site of protein

Computed Atlas of Surface Topography of Proteins (CASTp) (http://sts.bioe.uic.edu/castp/) is a web server that provides information about the active site, geometric and topological properties of Angiotensin-converting enzyme 2 (ACE2) receptors(PDB ID: 1R42) structures, including surface pockets, interior cavities [43], and cross channels, which are importance for proteins to carry out their functions. This study used the PDB ID (http://mmcif.wwpdb.org) to analyze the active site of protein by using the CASTp server [42].

Protein-protein docking

ClusPro tool (https://cluspro.org/) is most frequently utilized for protein-protein docking., it predicts the most likely binding interaction between two proteins ACE2 receptors of human cell and S protein of SARS-CoV2. This can be useful for studying biological functions that depend on protein interactions, such as enzyme-substrate binding, receptor-ligand interactions, and signaling pathways [44].

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Pathway analysis of ACE2 protein

The Kyoto Encyclopedia of Genes and Genomes pathway Database (https://www.genome.jp/kegg/pathway.html) detects the renin-angiotensin system (RAS) for ACE2 receptors of human cell. This database provides information about biological pathways, including metabolic, signaling, and cellular processes [45].

Results and Discussion

In this study, we looked into the levels of several crucial electrolytes in the blood (calcium, sodium, chloride, and potassium) in subjects who have recovered from COVID-19 and in apparently healthy subjects who have never been infected with SARS-CoV2 serving as the control group. The findings are reported in Table (1).

Table 1: Serum levels of some electrolytes with urea and creatinine in the study subjects

Parameter	Groups	Mean ± SD	*p-value*	*Normal value*
Sodium (mmol/L)	Recovered Patients (N = 200)	133.4 ± 2.92	0.000*	135-145 mmol/L
	Controls (N = 100)	140.3 ± 2.91		
Potassium (mmol/L)	Recovered Patients (N = 200)	3.35 ± 0.74	0.000*	3.5 – 5.0 mmol/L
	Controls (N = 100)	4.50 ± 0.61		
Calcium (mg/dL)	Recovered Patients (N = 200)	8.1 ± 1.07	0.000*	8.5 – 10.5 mg/dL
	Controls (N = 100)	9.2 ± 0.68		
Chloride (mmol/L)	Recovered Patients (N = 200)	102.3 ± 3.4	0.033*	98 – 106 mmol/L
	Controls (N = 100)	100.6 ± 3.3		
Urea (mg/dL)	Recovered Patients	38.7 ± 8.9		15 – 45 mg/dL

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	(N = 200)		0.009*	
	Controls (N = 100)	33.7 ± 7.7		
Creatinine (mg/dL)	Recovered Patients (N = 200)	0.99 ± 0.21	0.005*	0.6 – 1.2 mg/dL
	Controls (N = 100)	0.82 ± 0.31		

*Significant at the levels of ($p \leq 0.05$).

According to the table 1, there is a significant (*p-value* < 0.000) drop in blood calcium, sodium, and potassium concentrations (133.4 ± 2.92 mmol/L, 3.35 ± 0.74 mmol/L and 8.1 ± 1.07 mg/dL respectively) in the recovered subjects group compared to the control group (140.3 ± 2.91 mmol/L, 4.50 ± 0.61 mmol/L, 9.2 ± 0.68 mg/dL respectively). In addition, there is a significant increase in the serum levels of urea and creatinine (38.7 ± 8.9 mg/dL, p-value 0.009, 0.99 ± 0.21 mg/dL, p-value 0.005 respectively) in the recovered subjects group compared to the control group (33.7 ± 7.7 mg/dL, 0.82 ± 0.31 mg/dL).

Table (2) shows the number and percentage of cases presented with hyponatremia, hypernatremia, hypokalemia, hyperkalemia, hypocalcemia, hypercalcemia, hypochloremia and hyperchloremia in both the recovered subjects and control groups.

Table 2: The states of electrolyte disturbances in the study subjects

Groups	**Recovered Patients (N = 200)**	**Controls (N = 100)**
Hyponatremia N (%)	105 (52.5 %)	0 (0 %)
Hypernatremia N (%)	8 (4 %)	0 (0 %)
Hypokalemia N (%)	95 (47.5 %)	0 (0 %)
Hyperkalemia N (%)	0 (0 %)	0 (0 %)
Hypocalcemia N (%)	125 (62.5 %)	27 (27 %)

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Hypercalcemia N (%)	0 (0 %)	0 (0 %)
Hypochloremia N (%)	10 (5 %)	0 (0 %)
Hyperchloremia N (%)	15 (7.5 %)	5 (2.5 %)

(Hyponatremia < 135 mmol/L, hypernatremia > 145 mmol/L, hypokalemia < 3.5 mmol/L, hyperkalemia > 5.1 mmol/L, hypocalcemia < 8.5 mg/dL, hypochloremia < 96 mmol/L, hyperchloremia > 106 mmol/L).

As shown in table 2, the findings of the current investigation indicate that 105 (52.5 %) of the recovered subjects have hyponatremia, 95 (47.5 %) have hypokalemia, 125 (62.5 %) have hypocalcemia and 10 (5 %) have hypochloremia. In comparison, none of the subjects in the control group had hyponatremia, hypokalemia or hypochloremia and only 27 (27 %) had hypocalcemia. The results also show that only 8 (4 %) of the recovered subjects have hypernatremia and 15 (7.5 %) have hyperchloremia compared to only 5 (2.5 %) having hyperchloremia in the control group. None of the study subjects in both groups have hyperkalemia or hypercalcemia.

The results of the present study are in agreement with many previous studies that reported findings of electrolyte disturbances in patients with COVID-19, the most common disturbances being hyponatremia, hypokalemia, hypocalcemia and hypochloremia. However, those studies investigated electrolyte disturbances during the course of COVID-19 and before complete recovery from the illness. To our best knowledge, this is the first study to investigate electrolytes disturbances after full recovery from COVID-19 in order to establish whether or not electrolyte disturbances and their associated symptoms can be one of the long-term impacts of COVID19, and to explain at least in part the cause of some long term persistent COVID symptoms remaining even after full recovery from COVID-19.

Previous research has demonstrated that COVID-19 affects not only the respiratory system but also the GI tract, neurological, cardiovascular, and urogenital systems. A disturbance might result in an imbalance of electrolytes and fluid due to the fact that the GI tract and kidneys are critical to regulating fluid and electrolyte balance in the body. If left untreated, Poor equilibrium of electrolytes and fluids can be harmful [46].

Disturbances in fluid and electrolytes result from impaired renal function [47]. Additionally, fluid and electrolyte imbalances can result from GI problems (Of all prevalent kind is hypokalemia) [48]. The digestive tract and kidneys play critical roles in regulating electrolyte and fluid balance. Damage to them generally disrupts the equilibrium of fluids and electrolytes [49]. The cell entrance receptor ACE2, which is one of the important enzymes in the renin-angiotensin system and is used by COVID-19, has been hypothesized to cause fluid and electrolyte imbalances (RAS) [50, 51]. Some SARS-CoV2 infections have been documented to result in a condition of inappropriate antidiuretic hormone secretion (SIADH) in infected individuals, which results in fluid and electrolyte abnormalities [52].

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Problems of electrolytes in patients, including an imbalance of chlorine, potassium, sodium and calcium, have been confirmed by studies conducted on covid-19 [53,54]. One of among the most widespread abnormalities in electrolytes is hyponatremia, which is linked to an increased risk of mortality in hospitalized patients [55]. Case-control research found that COVID19 patients had higher rates of hypochloremia, hypokalemia, and hyponatremia compared to controls [56]. Hypokalemia, a COVID-19 complication, can exacerbate acute respiratory distress syndrome (ARDS) and place patients at danger for heart injury [57]. Another electrolyte problem that affects COVID-19 patients is hypocalcemia, which can be harmful if untreated and even raise mortality rates [58].

For the control of bodily processes and the maintenance of health, proper electrolyte balance is crucial. Even a small departure from normal electrolyte values can lead to various problems, including the possibility of death. A terrible side effect for hyponatremia sufferers is acute cerebral edema [59]. Patients who have hyponatremia may experience rhabdomyolysis, convulsions, mood instability, or even coma. If left untreated, hypokalemia is extremely damaging and has an impact on the neurohormonal activation, cardiovascular system and other key organs [60]. The primary negative consequence of hypocalcemia is elevated neuromuscular excitability, which can include muscle spasms, stinging in the arms and legs, and perioral numbness. In rare instances, hypocalcemia can also result in reversible cardiomyopathy [61]. Changes in chloride levels can also raise the danger of severe renal damage, morbidity, and even death [62].

Electrolyte imbalance, particularly in the cases of magnesium, potassium, and calcium, can produce arrhythmias and the potentially fatal polymorphic ventricular tachycardia known as torsades de pointes in COVID-19 patients [63,64]. Additionally, hypokalemia can cause cardiac and lung cells to become hyperpolarized, have an elevated resting potential, and depolarize, which can result in ventricular arrhythmia and respiratory failure [65]. Nausea, vomiting, weakness, and disorientation are typical symptoms of sodium variations, which are rarely localized to the heart and can cause seizures or coma if addressed. ECG alterations that are consistent are uncommon [66]. In the myocardial, sodium and potassium play a crucial role in regulating membrane potentials, which in turn controls cardiac action potentials. Contrary to potassium, however, changes in serum sodium levels rarely result in serious cardiac issues unless there has been a large departure from typical physiological norms [67]. The myocardium's cells are significantly impacted by calcium in terms of conduction, intracellular signaling, and muscle fiber contraction. Calcium concentrations in particular can modify the length of the plateau phase (phase 2) of the cardiac action potential and have an impact on heart conduction. This means that catastrophic disorders like malignant arrhythmia or cardiac arrest might result from disturbances in the calcium homeostasis [68,69]. Bicarbonate and chloride have an antagonistic interaction. Bicarbonate reabsorption frequently rises proportionally when serum chloride levels drop as a result of renal or gastrointestinal loss, leading to metabolic alkalosis. Vomiting and nasogastric suctioning are the two most typical gastrointestinal factors that contribute to hypochloremia. Hypochloremia typically manifests physically as the concurrent metabolic alkalosis. Cardiovascular arrhythmias, neuromuscular irritability, apathy, and disorientation [70,71]. Most of the symptoms noted from electrolytes imbalances include fatigue, cardiac arrhythmias, dyspnea and respiratory dysfunction, lethargy and cough. These symptoms are similar to some of the COVID19 symptoms and even to the long-term symptoms of COVID-19 remaining after recovery from the illness. Since we have found electrolyte imbalances in the recovered subjects after full recovery from COVID19, this might at least in

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part give a possible explanation for the long-term persistent symptoms of COVID-19 in some subjects even after full recovery.

Structure analysis

The surface of the SARS-CoV2 virus contains a glycosylated protein referred to as spike (S) protein, which plays a critical role in allowing the virus to infect human cells. This protein consists of three chains (A, B, and C) with lengths 1281 aa which divided into two subunits S1 subunit which contains the domain was responsible for recognizing and binding to host cell receptors known as the receptor-binding domain (RBD), while the S2 subunit is responsible for the merge of the viral membrane with the host cell membrane once the virus is bound to the receptor, Figure 1.

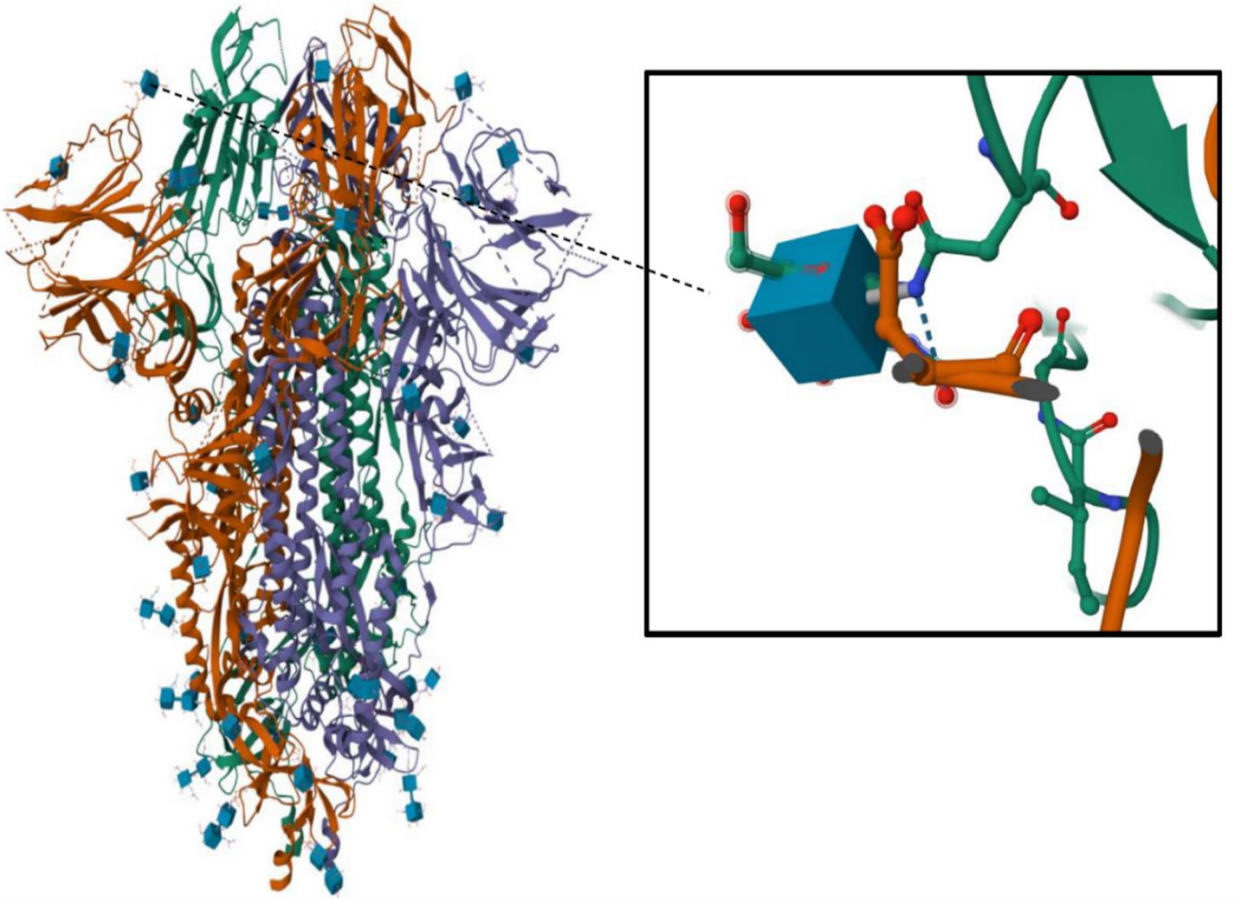

Figure 1: The quarterly structure of spike (S) protein that presented on the surface of the SARS-CoV-2 virus in the PDB entry (PDB ID: 6VXX), shown NAG (2-acetamido-2-deoxy-beta-D-glucopyranose-(1-4), by PyMol tool.

The surface of many human cells, particularly in the respiratory tract, heart, kidneys, and intestines, contains the ACE2 receptor, which plays an important role in regulating blood pressure and fluid balance by converting angiotensin II into angiotensin (1-7), which has vasodilatory effects, Figure 2.

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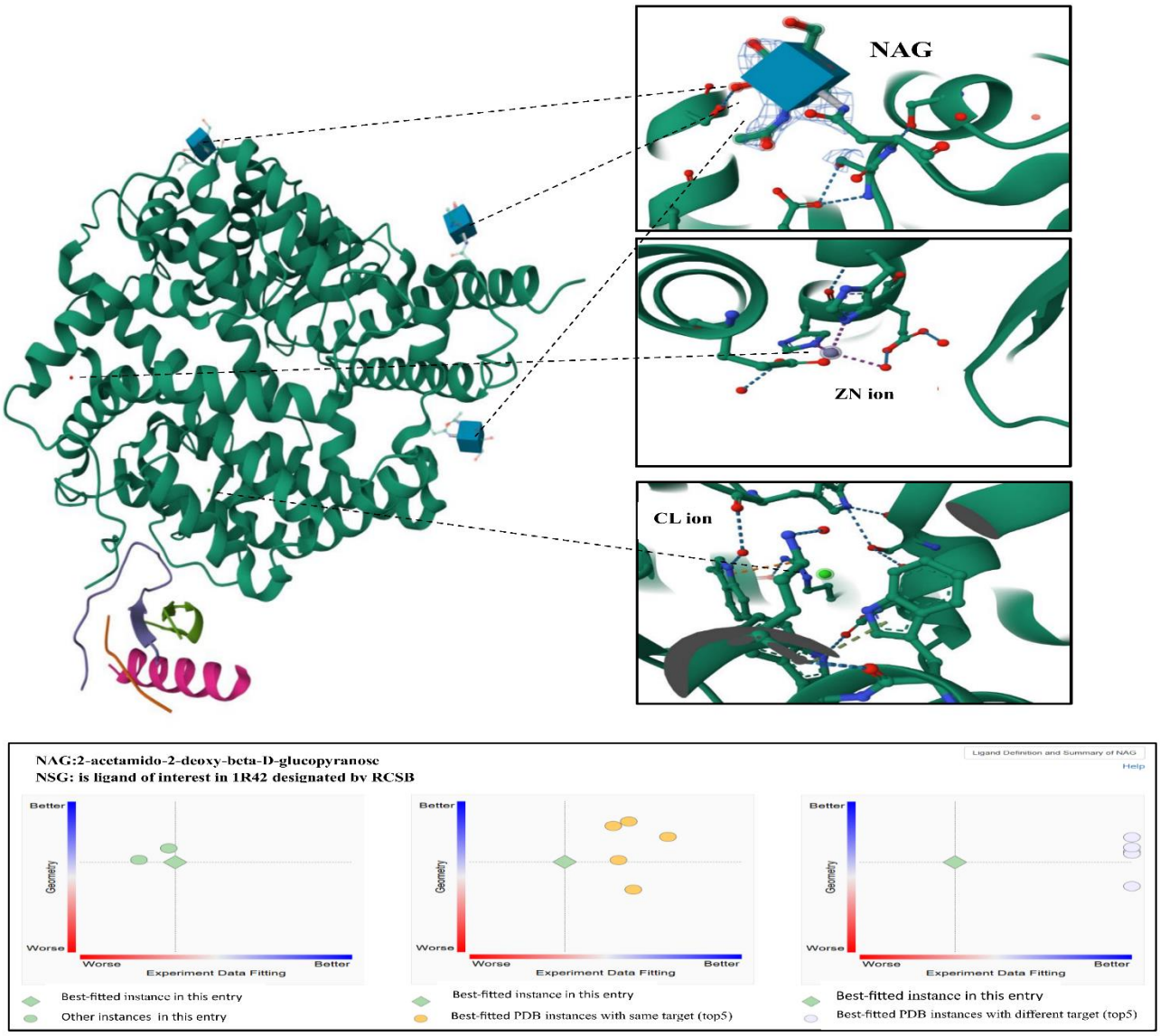

Figure 2: The quarterly structure of Angiotensin Converting Enzyme-Related Carboxypeptidase (ACE2) on the membrane of human cell (PDB ID: 1R42), shown NAG (2-acetamido-2-deoxy-beta-D-glucopyranose-(1-4), Cl ion and ZN ion, detect by PyMol tool.

The spike protein (specifically the RBD in the S1 subunit) attaches itself to the human cell surface's ACE2 receptor. Once the spike (peplomer) protein binds to ACE2, the virus undergoes a conformational modification that enables the viral envelope to merge with the membrane of the host cell, enabling the virus to release its RNA into the host cell. This leads to viral replication inside the host. For this reason, the spike protein of SARS-CoV2 and the ACE2 receptor is central to the viral entry process. The spike protein binds to ACE2 in human cells, allowing the virus to infect and replicate inside the host.

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Predicted the active site by CASTP

To identify and characterize the active site of 1R42 Native Human ACE2 consider the key steps to detect the relation with the other protein. The CASTpFold tool was used to detect the model structure active site of the protein as well as determine the amino acid residues active site. The top active site is determined in one of the largest area 4183.429 and volume of 8098.169 amino acids of 1R42. according to CASTp prediction, as shown in Figure 3.

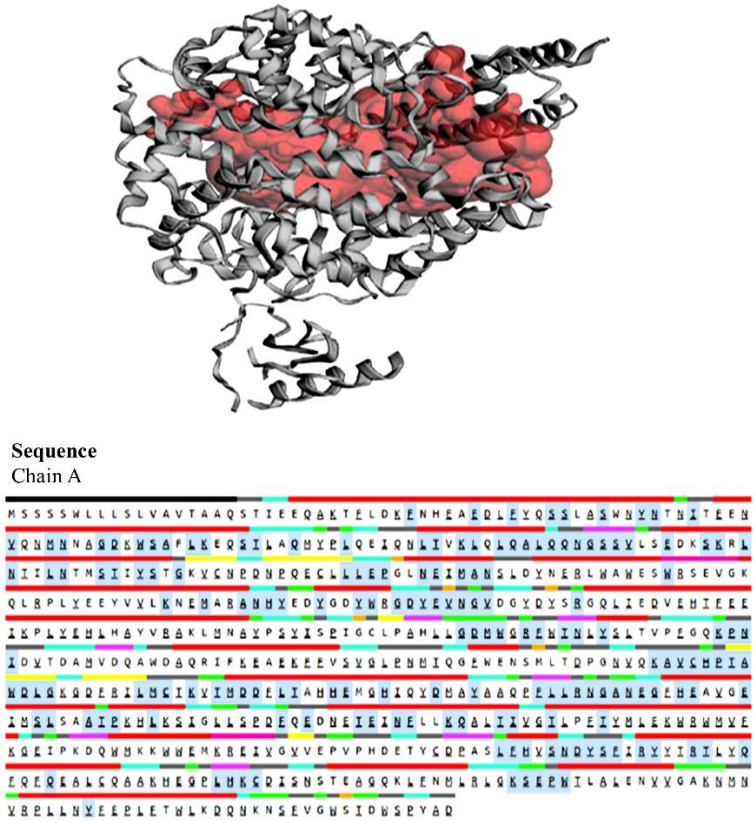

Figure 3: determine the active site of the structure of 1R42 (Receptor), the largest active site was found in the largest area of 4183.429 and volume of 8098.169 amino acids, via the CASTpFold tool.

The features such as active site, metal ion-binding site, binding site, glycosylation site and disulfide bond of Native Human ACE2 protein receptor, also detect the position on the amino acid sequence of protein, table 3.

Table 3: Features of Native Human Angiotensin Converting Enzyme-Related Carboxypeptidase (ACE2) PDB ID:1R42.

Feature	Position	Description	Reference
Active site	A: 357		Uniprot: Q9BYF1
Active site	A:505		Uniprot: Q9BYF1

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metal ion-binding site	A:374	Zinc; catalytic	Uniprot: Q9BYF1
metal ion-binding site	A: 378	Zinc; catalytic	Uniprot: Q9BYF1
metal ion-binding site	A: 402	Zinc; catalytic	Uniprot: Q9BYF1
binding site	A:169	Chloride	Uniprot: Q9BYF1
binding site	A:273	Substrate	Uniprot: Q9BYF1
binding site	A:345	Substrate	Uniprot: Q9BYF1
binding site	A:346	Substrate; via carbonyl oxygen	Uniprot: Q9BYF1
binding site	A:371	Substrate	Uniprot: Q9BYF1
binding site	A:477	Chloride	Uniprot: Q9BYF1
binding site	A:481	Chloride	Uniprot: Q9BYF1
binding site	A:515	Substrate	Uniprot: Q9BYF1
glycosylation site	A:53	N-linked (GlcNAc...) asparagine	Uniprot: Q9BYF1
glycosylation site	A:90	N-linked (GlcNAc...) asparagine	Uniprot: Q9BYF1
glycosylation site	A:103	N-linked (GlcNAc...) asparagine	Uniprot: Q9BYF1
glycosylation site	A:322	N-linked (GlcNAc...) asparagine	Uniprot: Q9BYF1
glycosylation site	A:432	N-linked (GlcNAc...) asparagine	Uniprot: Q9BYF1
glycosylation site	A:546	N-linked (GlcNAc...) asparagine	Uniprot: Q9BYF1
disulfide bond	A: 133-141		Uniprot: Q9BYF1
disulfide bond	A: 344-361		Uniprot: Q9BYF1
disulfide bond	A: 530-542		Uniprot: Q9BYF1

Interaction between ACE2 and S-protein

Features for (ACE2) domain, region, motif, compositional bias. Two domains make up the ACE2 enzyme's extracellular region. A zinc metallopeptidase domain (residues 19–611) is the first. The second domain, which is 48% identical to human collectrin, is found at the C-terminus (residues 612-740). There are 5 regions, three of which are crucial for the interaction with SARS-CoV spike glycoprotein, first region at position (30-41), the second one at (82-84) the third at (353-357), Figure 4.

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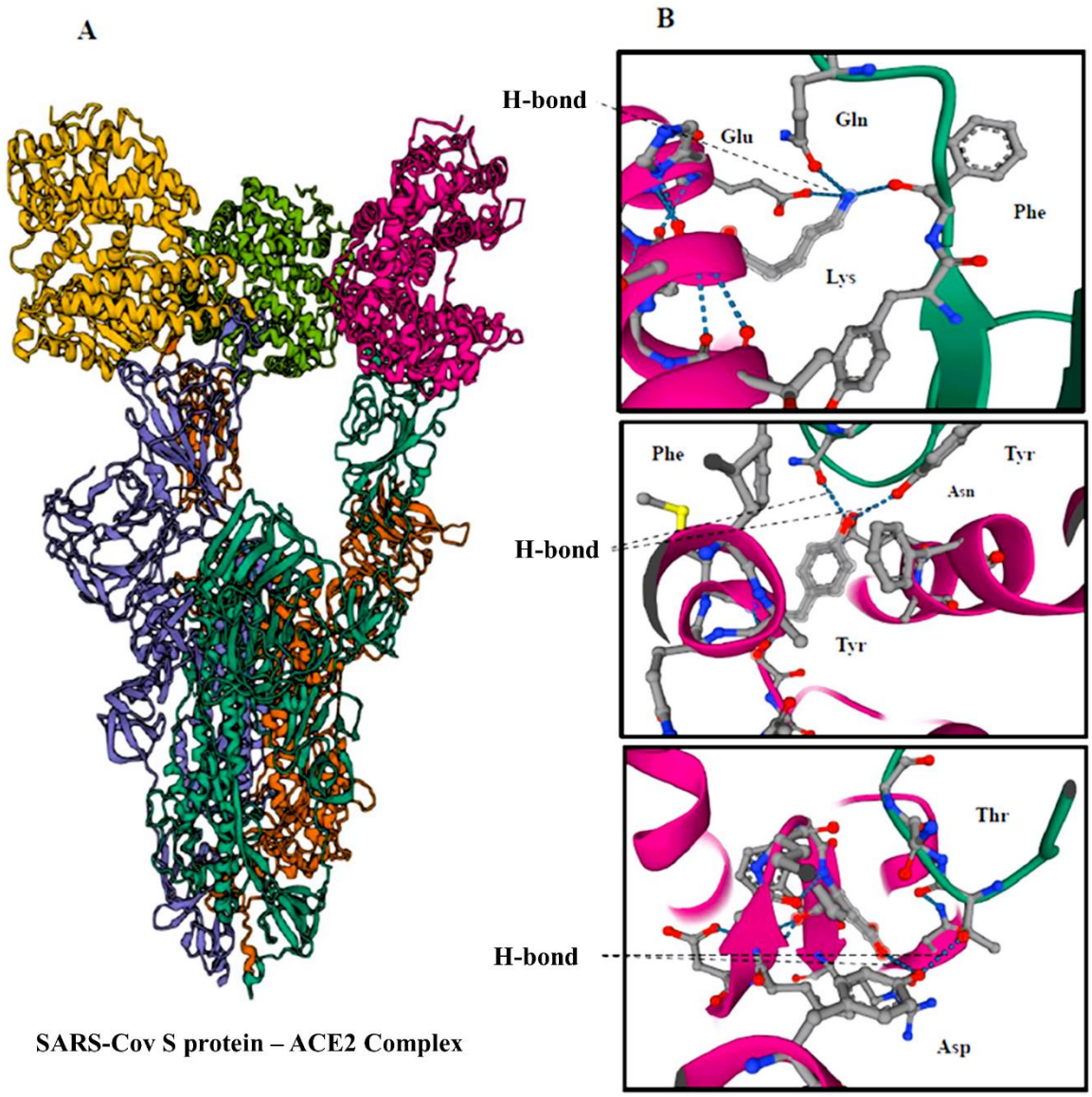

Figure 4: Shown (A) how the SARS-CoV spike glycoprotein interacts with ACE2 protein, The deposited structure is colored by the chain, top view. This structure contains copies of Spike glycoprotein; 3 copies of Processed ACE-2, detecting the three regions of interaction between the first copy of ACE2 protein (pink color) and spike glycoprotein (with green color), Pymol tool.

The first interaction which occurs at region (30-41) between Lys (K) at position 33 and Glu(E) at position 37 on ACE2 protein interaction by hydrogen bonds with Phe(F) at position 521 and Gln(Q) at position 524 of spike glycoprotein (S protein), the second interaction which occurs at region (82-84) between Tyr(Y) at position 85 of ACE2 protein with Phe(F) at position 517, Asn (N) at position 518 and Tyr(Y) at position 520 of S protein; the third interaction which occur at region (353-357) between Asp(D)at

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position 357 of ACE2 by hydrogen bond with Thr (T) at position 531 of spike glycoprotein. This Interaction between ACE2 and S protein is responsible for SARS-CoV interaction with human cells, table 4.

Table 4: Features of ACE2 protein and region interacting with SARS-CoV spike glycoprotein.

Types	Position	Description
Domain	19-607	Peptidase M2
Domain	614-805	Collectrin-like
Region	30-41	Interaction with SARS-CoV spike glycoprotein
Region	82-84	Interaction with SARS-CoV spike glycoprotein
Region	353-357	Interaction with SARS-CoV spike glycoprotein
Region	652-659	Essential for cleavage by ADAM17
Region	772-805	Disordered
Motif	778-786	LIR
Motif	781-784	Endocytic sorting signal
Motif	781-785	SH2-binding
Motif	792-795	PTB
Motif	803-805	PDZ-binding

On the other hand, the third interaction for more specific information about the interaction which occurs between Asp (D) at position (357) binding by hydrogen bond with Tyr (Y) at position 43 that interaction with Thr (T) at position 531 by hydrogen bond this interaction make SARS-CoV spike glycoprotein more complex interaction with ACE2 protein, Figure 5.

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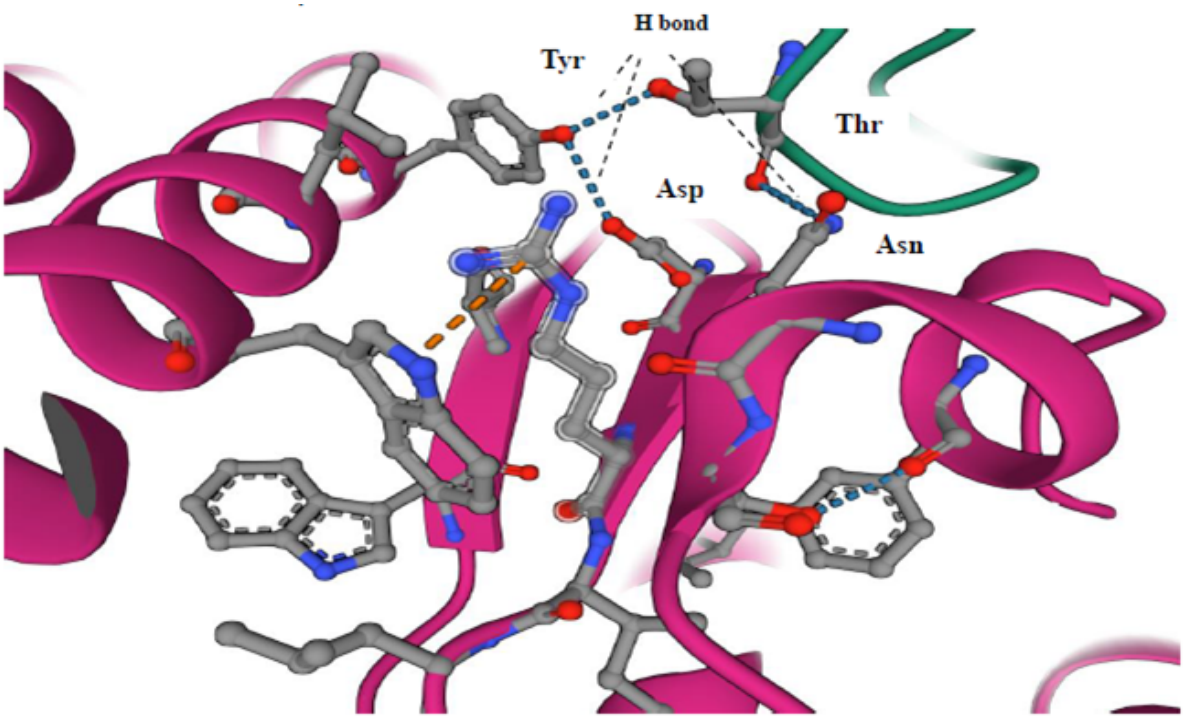

Figure 5: Shown the complex interaction between SARS-CoV spike glycoprotein (green color) with ACE2 (pink color) protein.

Pathway analysis of the ACE2 receptor

Angiotensin-Converting Enzyme-Related Carboxypeptidase (ACE2), the protein encoded by the ACE2 gene, is a member of the angiotensin-converting enzyme family of dipeptidyl carboxypeptidases, and it shares many similarities with the human angiotensin-converting enzyme. Numerous human organs have been shown to express ACE2, and its expression in specific organs and cells raises the possibility that it regulates fertility, cardiovascular health, and renal function [72]. The membrane-bound enzyme ACE2 is mostly expressed in the heart, kidneys, intestines, and lungs. It is an essential regulator in the Renin-Angiotensin-Aldosterone System (RAAS), a key hormonal pathway involved in maintaining electrolyte balance and fluid homeostasis. When the renin enzyme breaks down its substrate angiotensinogen (Agt) into the decapeptide angiotensin I, which is subsequently broken down by the ACE, angiotensin II (Ang II), a crucial part of the classical RAS, is created. The AT1 receptor is activated by Ang II. Most of the known effects of Ang II in the kidney, such as renal sodium (Na+) reabsorption, vasoconstriction, and aldosterone secretion, are mediated by this primary receptor. As a result, hypertension is exacerbated by elevated blood pressure. In addition to the axis of (ACE)/Ang II/AT1R and AT2R, other signaling pathways in the RAS, such as ACE2/angiotensin-(1-7)/Mas and Ang IV/IRAP, and other RAS active peptides, with physiological significance as Ang III, Ang A and almandine, are now well known recognized.

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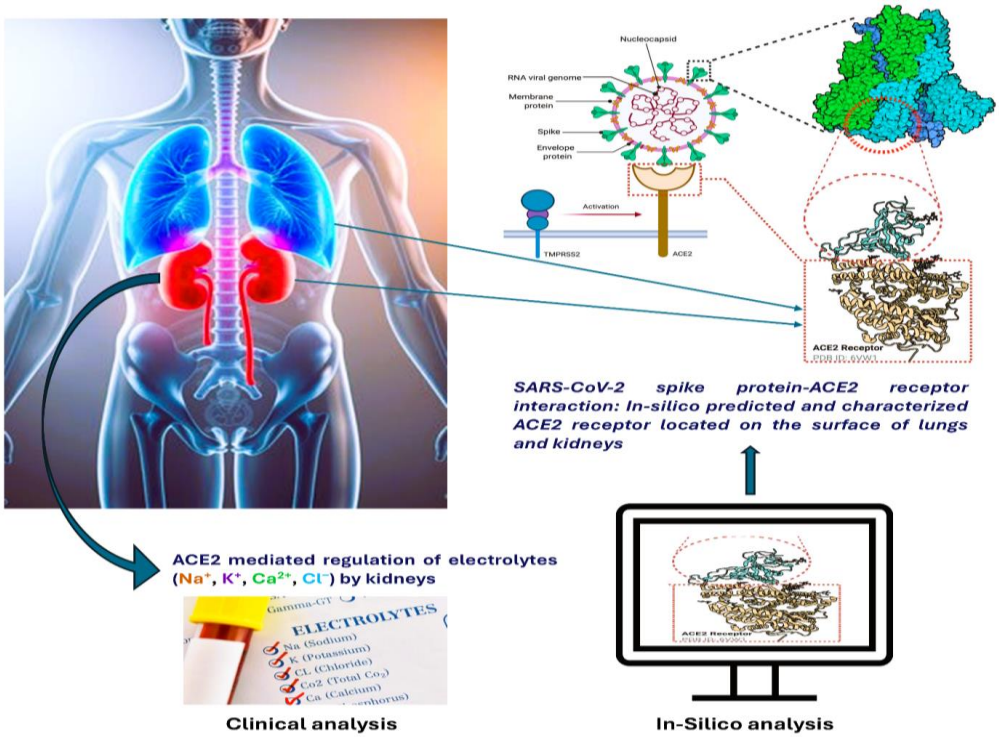
The most crucial function of ACE2 is regulating the balance of electrolytes, particularly sodium (Na^+), potassium (K^+), and water. It does this by blocking the effects of angiotensin II, a key molecule in the RAS, which plays a crucial role in regulating blood pressure and fluid balance. ACE2 acts by converting angiotensin II into angiotensin (1-7), a peptide that has vasodilatory effects, lowering blood pressure and promoting natriuresis. This action is responsible for balancing blood pressure and maintaining appropriate fluid and electrolyte levels. When the SARS-CoV-2 spike (Peplomer) protein binds to ACE2 in human kidney cells, it disrupts the normal function of the ACE2 protein receptor. Specifically, ACE2 is internalized and degraded after binding to the virus, resulting in a decrease in its activity. This results in an imbalance between angiotensin II and angiotensin (1-7), which has important implications for fluid balance and electrolyte regulation. So, when the activity of ACE2 is reduced, it leads to less transformation of angiotensin II into angiotensin (1-7). high levels of angiotensin II can lead to vasoconstriction, increased aldosterone secretion, and increased sodium retention in the kidneys. This can cause increased blood pressure and fluid retention, potentially leading to a disruption in the sodium balance. The high level of angiotensin II also stimulates the secretion of hormone (aldosterone) that promotes reabsorption of sodium and excretion of potassium by the kidneys. high level of aldosterone can lead to decrease potassium levels (hypokalemia) as potassium is excreted in the urine to maintain sodium balance. The imbalance in signaling of the angiotensin- renin system is because of ACE2 disruption which leads to fluid retention. Aldosterone and angiotensin II work together to increase sodium reabsorption in the kidneys, which can lead to water retention and edema (swelling).



Graphical Abstract

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Conclusions

Our findings conclusively show that recovery from COVID-19 does not always mean an immediate return to physiological normalcy; significant imbalances in electrolytes such as sodium, potassium, and calcium were found to persist for at least two months. These clinical realities may underpin many of the long-term symptoms reported by survivors. Complementing these observations, our in-silico modeling revealed the precise molecular interactions—specifically, how the SARS-CoV-2 spike protein engages with critical ACE2 receptor domains (30-41, 82-84, 353-357)—that can disrupt ACE2's crucial function in maintaining the body's fluid and electrolyte balance. These clinical and computational findings provide strong justification for the persistence of these electrolyte disturbances. To enhance long-term health results for COVID-19 patients, we must understand how viral infections disrupt essential body systems because this will lead to necessary monitoring and intervention efforts to correct electrolyte imbalances.

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