Int J Basic Sci Med. 2023;8(1):30-35 Original Article

http://ijbsm.zbmu.ac.ir/ doi 10.34172/ijbsm.2023.05

Investigating the Relationship Between High Levels of Angiotensin II in Plasma and the Rate of Deterioration in Hypertensive Patients to COVID-19

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ARTICLE INFO
Article History:
Received: March 15, 2023
Accepted: March 24, 2023
Published online: March 29, 2023

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Abstract

Introduction: The COVID-19 crisis poses a heightened risk to vulnerable populations. Considering factors influencing deterioration, complications, and mortality, it is especially important to pay attention to these groups, including persons with hypertension (HTN) and diabetes. This study aimed to investigate the correlation between the angiotensin II (ANG II) level and the disease severity and clinical course in COVID-19 patients.

Methods: A cross-sectional study was conducted on 50 COVID-19 patients (mean age 59.1 ± 20) admitted to Sinai hospital in Hamedan. The blood samples of the patients were taken during hospitalization and discharge, and the plasma ANG II level was measured using an enzyme-linked immunosorbent assay kit. The quantitative comparison was analyzed with paired *t* test and qualitative comparison with the chi-square test. The correlation of variables was checked with the Pearson test, and $P<0.05$ was considered statistically significant.

Results: Overall, 44%, 16%, and 10% of COVID-19 patients had HTN, cardiovascular disease (CVD), and 10% diabetes, respectively. The oxygen level of 82% of the patients was below 90, of which 68% were intubated, and the lowest oxygen levels were observed in patients with HTN and CVD with 2 deaths. The primary and secondary examination of the ANG II level demonstrated that its level was significantly higher during illness compared to full recovery and decreased during recovery.

Conclusion: The ANG II level is related to the severity of the disease in the early stages of 2019-nCoV infection. Therefore, HTN or other diseases that affect the level of ANG II in the blood can increase the severity of the disease.

Keywords: Angiotensin-converting enzyme 2, Angiotensin II, COVID-19, Hypertension

Please cite this article as follows: Shahnazari M, Majzoobi MM, Keramat F, Mohammadi Y, Najafi R, Ghasemi Basir HR, et al. Investigating the relationship between high levels of angiotensin ii in plasma and the rate of deterioration in hypertensive patients to COVID-19. Int J Basic Sci Med. 2023;8(1):30-35. doi:10.34172/ijbsm.2023.05.

Introduction

Due to the mutations caused by the coronavirus disease 19 (COVID-19) in populations, the instability of immunity caused by vaccination, and the complications caused by this disease, this disease has become a public health crisis in the world.[1] Therefore, paying attention to the mechanism of action and the group at risk is of special importance. COVID-19 is the seventh member of the Coronavirus family, which belongs to breed B of the dark beta virus. This family includes severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV). Compared to the lethal rate of 10% SARS-CoV and 37% lethal MERS-CoV,[2-4] 2019-nCoV has so far been introduced as the third deadly virus in the Coronavirus family. According to initial reports, most patients with COVID-19 have a history of

hypertension (HTN), kidney disease, cardiopulmonary disease, and diabetes.[5-7] A study of 45 000 patients with COVID-19 in China reported that the mortality rate for patients without any underlying disease was about 0.9%, while the mortality rate in patients with cardiovascular disease was 10.5%. The corresponding rate was 7.3% and 6.3% in diabetic and HTN patients, respectively.[8] Earlier research on sepsis, aspiration, and MERS caused by the CoV has also suggested that renin-angiotensin system (RAS) dysfunction is involved in the molecular pathogenesis of acute respiratory distress syndrome.[9,10] The need to identify biomarkers for severe disease prediction and fatality messages is highlighted when patients have co-morbidities such as pulmonary and cardiac diseases, renal disease, and HTN, and this is an increasing and accelerating factor for the progression of the disease. These cases show a sensitive population and a higher rate of morbidity and mortality that can be considered among sensitive populations.[7] Angiotensin-converting enzyme 2 (ACE2), which is involved in the RAS, is expressed on the surface of the epithelial cells of the alveoli in the lung and other tissues. ACE2 is also the receptor of the coronavirus. The binding of the spike protein of this virus to ACE2 leads to the proteolytic degradation of ACE2 by serine protease 2, facilitating the entry of the virus into cell.[10]

ACE2 converts angiotensin II (ANG II) to ANG 1-7 and reduces blood pressure (BP) by dilating blood vessels and excreting sodium. It also decreases inflammation through the production of nitric oxide. These effects are opposite to those caused by ACE-Ang II signaling. ACE converts ANG I to ANG II. ANG II increases BP by constricting blood vessels and increasing renal sodium reabsorption, leading to increased inflammation and fibrosis.[3,11] ANG II accelerates atherosclerosis, inflammation, oxidative stress, and migration of endothelial cells. According to several recent studies, the identification of ACE2 as a receptor for the coronavirus led to the creation of new therapeutic methods to block this enzyme or reduce its expression to prevent the virus from entering and causing infection in tissues that express ACE2, including the lung, heart, kidney, brain, and intestine.

In the study conducted by Ramchand et al on COVID-19, it was hypothesized that the increased activity of ACE-Ang II, compared to ACE2-Ang-(1-7), may cause acute lung damage in patients. ANG II causes lung inflammation and infection by activating the ANG I receptor (AT1R). Reducing the production of ANG II following the use of ACE inhibitors or inhibiting the activity of Ang II-AT1R increases the production of ANG 1-7 by ACE2, which ultimately reduces inflammation and fibrosis.[12] According to a report by Beyerstedt et al, this can lead to new treatments to prevent or reduce the expression of the enzyme to prevent the virus from entering and infecting tissues such as the lungs, heart, kidneys, brain, and intestines that express ACE2.[13] In another study, Razeghian-Jahromi et al found that ACE2 activity is specifically impaired in cardiovascular patients, and this enzyme is used by the coronavirus to initiate infection.[14] Huang et al also concluded that the use of RAS inhibitors in heart patients leads to an increase in ACE2, which may increase the severity of cardiovascular disease (CVD) in these patients.[15] However, there is evidence that coronary infection decreases ACE2 levels, which may lead to increased ANG II expression and thus increased respiratory distress.[16] According to the relationship between 2019-nCoV and the level of ANG II, it seems that the deterioration and course of the disease of COVID-19 are also related in people with high BP or heart diseases. Although studies have been performed in this case, due to confusing effects, it has had contradictory results.

Based on inconsistencies reported regarding the association of high levels of ANG II with COVID-19 infection in people with underlying diseases such as HTN, cardiovascular disease, and diabetes, our samples were selected from a group of patients with COVID-19 during and after the disease. Complete recovery was used to find answers to questions such as 'whether RAS dysfunction is present in most patients with COVID-19' and 'which group of patients has high-risk conditions'. Accordingly, this study sought to investigate the relationship between morbidity and mortality and the course of the disease with the level of ANG II in patients with COVID-19.

Methods

A cross-sectional study was conducted on patients hospitalized in the corona intensive care unit (ICU) from March 1399 to July 1400 at Sina hospital in Hamedan, and the sample size was calculated using NCSS-PASS11 software. Assuming a minimum difference in ANG levels between the two groups and a standard deviation of 60, including an error of 1% and a power of 95%, the number of 50 people per group (total of 102 people) was needed, which was approved by the Ethics Committee of Hamedan University of Medical Sciences and then was approved and registered with code IR.UMSHA REC.1399.165. Written consent was obtained from all patients according to the rules of the ethics committee. Patients whose positive diagnosis of COVID-19 was confirmed by the polymerase chain reaction with nasal and pharyngeal swab samples were included in this study. Patients under 18 years of age were excluded from the study. First, the patient's complaints were questioned, and then a complete examination was performed, especially in terms of the level of consciousness, vital signs, pulmonary, and the like. The patient's oxygen saturation was measured and recorded, and then a computerized tomography scan was taken from the patient's lungs. Patients were admitted to imaging based on the level of oxygen saturation, severity of symptoms, and level of

involvement. One of the daily evaluations was to measure the percentage of oxygen saturation, and if it reached an acceptable level, it was decided to discharge the patient without receiving oxygen. The total obtained information including demographic characteristics (age, gender, and weight) of patients, clinical signs and symptoms (fever, pulse and respiration rate, BP, lung auscultation, and laboratory findings were recorded in special checklists. The laboratory findings included complete blood count, *erythrocyte sedimentation rate*, *C-reactive protein*, alanine aminotransferase, aspartate aminotransferase, *bilirubin*, prothrombin time, international normalized ratio, partial thromboplastin time, albumin, *creatine phosphokinase*, *lactate dehydrogenase*, *blood urea nitrogen*, *creatinine*, and the like. Then, we monitored and followed the outcome of the patients until the end of the hospitalization period in terms of hospitalization in the ICU, the need for intubation, recovery, and death. In addition to blood sampling for tests that are part of the routine examinations of hospitalized patients, about 5 cc of venous blood was collected in sterile tubes with the consent of all patients. To investigate whether changes in ANG II levels in patients with 2019-nCoV were associated with the worsening of the disease process, blood samples from the same patients were collected and assayed during recovery and one week after hospital discharge. For the first and second sampling of patients, after 10 minutes of rest, 5 mL of blood was collected on ice in tubes containing ethylenediaminetetraacetic acid, then it was centrifuged for 10 minutes at -4 ˚C, and the plasma was collected and stored at -80 ˚C until assayed in a batch (approximately 2 weeks between sampling and assay). The second sample was taken from the patients one week after discharge in the hospital laboratory and stored and evaluated according to the protocol. ANG II levels were measured using an enzyme-linked immunosorbent assay kit according to the manufacturer's instructions (ZellBio, Germany). All tests were performed repeatedly in the safety level 2 laboratory. Data were analyzed with SPSS software (version 22), and descriptive analysis and central tendency (means and standard deviations) were used for basic data. The quantitative and qualitative comparisons of variables between groups were performed with paired *t* test and Pearson chi-square test, respectively. The relationship between the variables in the two groups was investigated using Pearson's test, and a *P* value less than 0.05 was considered a statistically significant cutoff.

Results

Comparing the distribution of patients, it was found that 22 (44%), 8 (16%), and 5 (10%) patients had HTN, cardiovascular disease, and diabetes, respectively, and the remaining cases suffered from diseases such as thyroid and respiratory diseases, and blood fats. The most common underlying disease was HTN. Overall, 21 patients (42%) were females, while 29 patients (58%) were males, and their average age was 59 ± 1.20. In addition, the average age of male and female patients was 60.43 ± 19 and 57.36 ± 16.5, respectively (Table 1).

During the hospitalization period, the patients were divided into 6 groups based on the amount of oxygen saturation (Tables 2 and 3). In general, regardless of the type of underlying disease, 82% of hospitalized patients had an oxygen level below 90, of which 68% were intubated. Of these cases, about 46% and 24% in group 5 had O_2 saturation levels between 80% and 90%, as well as 80% and 70%, respectively, while about 12% of them had O_2 saturation levels below 70. Most of the cases requiring intubation and having low oxygen levels were in high BP and cardiovascular and elderly people. Only 2 deaths were observed in the people under observation for this research, who had heart disease and BP, while there was no death in people with other underlying

Table 1. Characteristics of 35 Patients With H7N9 Virus Infection

Age	N/Frequency	Value
Median (range)-year	50	(38-78) 59.1
Female gender, No. (%)	21	42.0
Male gender, No. (%)	29	58.0
Diabetic	5	10.0
Hypertension	22	44.0
Cardiovascular disease	8	16.0
Respiratory disease	3	6.0
Asthma	4	8.0
Hypothyroidism	4	8.0
Hyperlipidemia	3	6.0

Table 2. Classification of Patients Based on the Saturated Oxygen Level

O_2 Saturation		Frequency	Percent	Valid Percentage	Cumulative Percentage
Valid	Blew 50 degrees	4	8.0	8.0	8.0
	Between 50 and 60 degrees	1	2.0	2.0	10.0
	Between 60 and 70 degrees	1	2.0	2.0	12.0
	Between70 and 80 degrees	12	24.0	24.0	36.0
	Between 80 and 90 degrees	23	46.0	46.0	82.0
	Above 90 degrees	9	18.0	18.0	100.0
	Total	50	100.0	100.0	

diseases. The level of oxygen saturation in patients with high BP, cardiovascular disease, and diabetes, compared to other patients who have other underlying diseases, was at lower levels (mainly in groups 3 and 4). There was a significant difference between the two groups in terms of measurement (Table 4).

In this study, there was evidence for an association between increased levels of ANG II and COVID-19. It was found that the possibility of disease progress toward deterioration and worsen over time, oxygen saturation, and lung involvement can be due to the increase in the high level of ANG II. In other words, the examination of ANG II levels in patients with COVID-19 during hospitalization and after recovery and discharge from the hospital demonstrated that the level of ANG II in patients with 2019-nCoV in the first week of the disease was relatively higher than in the full recovery of the same patients. This level decreased mainly 4 weeks after the onset of the disease and in the state of complete recovery. These data revealed that ANG II levels may be related to the severity of the disease in the early stages of 2019-nCoV infection. Moreover, there was a significant difference between the plasma ANG II levels in different time periods (two stages of hospitalization and full recovery) of patients with 2019-nCoV (Table 5 and Figure 1). Our findings represented that the diagnosis of ACE2 as a CoV receptor is true with increased ANG II levels in patients with HTN, diabetes, and heart disease. There is a positive linear relationship between the levels of ANG II in patients with COVID-19 and the severity score of the disease, and the level of ANG II can be considered an important indicator to identify the complications, lethal effects, or prognosis of this disease.

Discussion

The present study investigated the relationship between the plasma level of ANG II and the deterioration and course of the disease in people with high BP and cardiovascular diseases with COVID-19. In general, 50 patients with COVID-19 were examined in terms of disease exacerbation and the need for intubation, and the level of ANG II during hospitalization and after recovery. The results indicated that the level of ANG II in human blood in two stages of hospitalization recovery is associated with the severity of disease caused by 2019-nCoV and the increased likelihood of requiring intubation and can predict disease severity as a marker for this group of patients.

ANG II is an active octapeptide and a potent vasopressor that, in addition to increasing adhesion molecules, cytokines, and chemokines,[17] has a proinflammatory effect on endothelial cells and vascular smooth muscle

Table 3. Descriptive Statistics of O_2 Saturation Levels in Patients Before and After Recovery

	N	Minimum	Maximum	Mean	Std. Deviation
O_2 saturation during the hospitalization	50	68.00	95.00	85.3600	5.87891
O_2 saturation after discharge from hospital	50	91.00	98.00	95.2400	1.49229
Valid N (listwise)	50				

Note. Std. deviation: Standard deviation.

Table 4. Paired T-test Results of Primary (During Hospitalization) and Secondary (After Discharge) O_2 Saturation

Disease	O_2 Saturation	No.	Mean	SD	95% CI of the Difference		t	Sig. (2-tailed)
					Lower	Upper		
Diabetes	Primary	5	-15.00000	3.93700	-25.93088	-4.06912	-3.810	0.019
	Secondary	5						
Hypertension	Primary	22	-13.77273	5.71491	-16.30658	-11.23888	-11.304	0.000
	Secondary	22						
Cardiovascular disease	Primary	8	-14.87500	6.24357	-20.09475	-9.65525	-6.739	0.000
	Secondary	8						

Note. No.: Number; SD: Standard deviation; Sig.: Significance; CI, confidence interval.

Table 5. T-test Results

		No.	Min.	Max.	Mean	SD	95% CI Difference		t	Sig. (2-tailed)
							Lower	Upper		
Descriptive statistics	Age	50	38	78	59.1400	9.34598	-	-		
	Elisa	50	0.22	0.49	0.3390	0.05982	-	-		
Paired samples statistics	Elisa1 (the first week of illness)	50	-	-	0.3390	0.05982				
	Elisa2 (After complete recovery)	50	-	-	0.3046	0.04932				
	Elisa1 - Elisa2	-	-	-	0.03442	0.07086	0.01428	0.05456	3.435	0.001

Note. No.: Number; SD: Standard deviation; Min.: Minimum; Max.: Maximum; Sig.: Significance; CI, confidence interval.

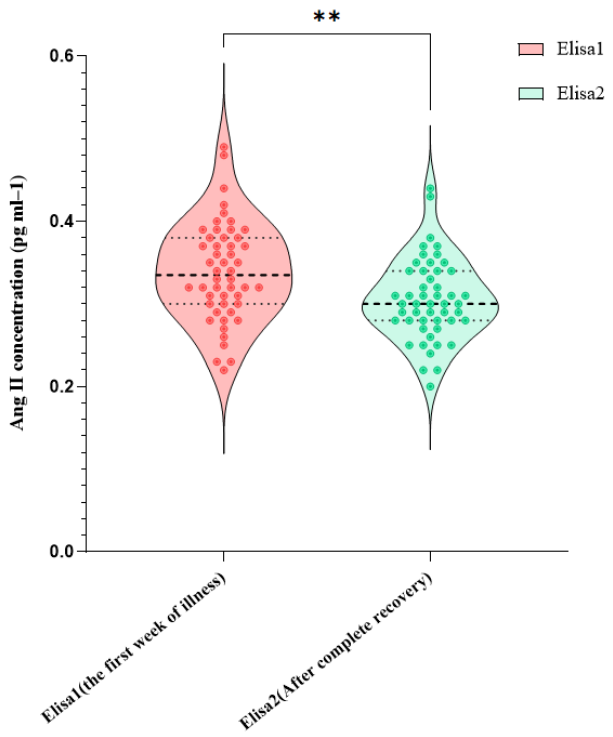

Figure 1. Angiotensin II Levels in the Plasmas of COVID-19-Infected Patients. *Note*. COVID-19: Coronavirus disease 19; HTN: Hypertension; CVD: Coronary heart disease. Angiotensin II levels in the plasma of recovered people from COVID-19 as controls, patients' group during COVID-19 infection. The number of infected individuals for each group was days 0-7 (HTN: n = 22, CVD: n = 8, Diabetes: n = 5, and other people with underlying diseases such as asthma and the like: n = 14) and 14-28 (The same patients with the specified number) groups. The horizontal lines represent the median value in each group. Detailed statistical information is provided in Table 5.

cells, increasing BP by constricting blood vessels and increasing sodium reabsorption from the kidneys, leading to increased inflammation and fibrosis.[3,11,18] It is also introduced as the main platform for RAS. Another important enzyme in this pathway is ACE2, which is known as the CoV receptor. The binding of the viral spike protein to ACE2 leads to the proteolytic degradation of ACE2 by serine protease 2 and facilitates virus entry into cell.[19] Based on this hypothesis, several ACE2-based therapies have been proposed, including vaccines based on the interaction of spike proteins and ACE2, inhibition of protease activity, blockade of the ACE2 receptor, and the use of a soluble form of ACE2.[19-21] There is scientific uncertainty regarding the use of ACE inhibitors and ANG receptor blockers (ARBs), which may increase the risk of COVID-19 and CVD.[22] In a study, Ni et al showed that restoring the balance between RAS and ACE2/angiotensin-(1-7)/MAS may help reduce organ damage in COVID-19.[23] On the other hand, there is limited evidence suggesting changes in plasma or pulmonary ACE2 levels. In a study by Biberoğlu et al, it was reported that ANG II and ACE2 levels in COVID-19 patients were not affected by HTN.[24] In other words, until now, the importance of ACE2 expression on the pathogenesis of COVID-19 and mortality is not exactly known, as Patel et al also acknowledged this issue.[25]

In our study, the levels of ANG II were completely related to the severity of the disease in the early stages of the 2019-nCoV infection, representing that people with high BP, cardiovascular diseases, and diabetes are among the high-risk groups in conditions infected with the coronavirus. Since fatal outcomes and disease course are usually due to the influence of several factors, potential confounding factors such as genetic background, gender, and immunodeficiency cannot be ruled out, which may lead to a significant impact on study conclusions because these factors may affect a person's vulnerability to COVID-19 and its severity. One of the limitations of this study is the small number of affected patients, and it seems that the relationship between the process, the severity of the disease, and its fatal outcome with changes in a single protein in human plasma is difficult. A suitable group is needed for standard statistical analyses. Therefore, there is a need for studies that address the potential benefits and harms of starting ACE inhibitors or ARBs as treatment for patients with COVID-19 with a larger number of cases.

Conclusion

According to the findings of this study, the level of ANG II in the first week of the disease was significantly higher in the blood of COVID-19 patients with diseases such as high BP, heart disease, and diabetes. Therefore, high BP or other diseases (diabetes and the like) affecting the level of this type of blood protein can increase the severity of COVID-19, which can be an alarm for clinical care. Our results suggest a therapeutic strategy that involves reducing ANG II levels during 2019-nCoV infection. Consequently, the use of ACEIs or ARBs may be beneficial in the management of hypertensive patients with COVID-19.

Acknowledgements

We appreciate our colleagues from Hamadan University of Medical Sciences.

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Competing Interests

None.

Funding

This work is supported by a grant from Hamadan University of Medical Sciences, Hamadan, Iran
IR.UMSHA.REC.1399.165.

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