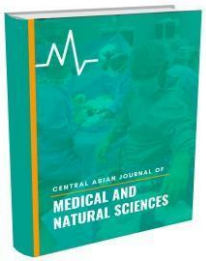

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Article

The Effect of Antihypertensive Drugs on the Serum Level of Angiotensin-Converting Enzyme 2 (ACE2) in Hypertensive Patients with Severe COVID-19 Infection

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Abstract: Although many studies were conducted worldwide on the effect of angiotensin converting enzyme inhibition on the morbidity and mortality of the patients with COVID-19, these studies have varied in their conclusions due to differences in populations, races, and ethnicity. This work aimed to study the effect of different antihypertensive drugs on the serum level of angiotensin-converting enzyme-2 in severely infected COVID-19 patients with hypertension. This study was conducted in Al-Nahrain University/College of Medicine/Chemistry and Biochemistry Department and Al-Mustansyria University /College of Medicine / Department of Medicine, Baghdad, Iraq. The study included 50 patients with confirmed severe COVID-19 infection: 25 COVID-19 patients with hypertension administered to the hospital, and 25 COVID-19 patients without hypertension administered to the hospital during the period from January, 2022 to September, 2022. The hypertensive patients were on angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) or Calcium-channel blockers or beta blockers prior to COVID-19 infection. The median level of angiotensin converting enzyme-2 (ACE2) in hypertensive patients was 3.22ng/ml (range 1.34-6.89 ng/ml) compared with0.89 ng/ml (range 0.22-1.35 ng/ml) in non-hypertensive group, with a highly significant difference. The study also showed a significantly higher level of serum ACE2 in patients on ACE inhibitors (median= 4.85 ng/ml, range= 3.22-6.89 ng/ml) than either of hypertensive patients taking ARBs (median= 2.56 ng/ml, range= 2.27-4.34 ng/ml) or those on Ca-channel blockers (median= 2.43 ng/ml, range= 1.34-4.39 ng/ml) with significant differences. It was also observed that patients on ARBs displayed the lowest concentration of D-dimer. This study showed that the use of antihypertensive drugs (ACE inhibitors or ARBs or Ca-channel blockers) prior to the infection with COVID-19 was not associated with the severity of disease and therefore, should not be discontinued during the course of infection.

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

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1. Introduction

Angiotensin-converting enzyme (ACE) is a zinc metallopeptidase that converts the weak vasoconstrictor angiotensin I (Ang I) into the more potent vasoconstrictor angiotensin II. It is an essential element of the renin-angiotensin system (RAS) (Ang II). Angiotensin-converting enzyme (ACE) is a crucial target for hypertension control, and ACE inhibitors, as the primary treatment for high blood pressure, have shown the most significant effect among cardiovascular agents. Numerous studies indicate that SARS-CoV and SARS-CoV-2 utilise ACE2 as an essential cellular receptor for facilitating infection.

SARS-CoV-2 and SARS-CoV exhibit 79 percent nucleotide sequence similarity. (Wang et al., 2020).

Computer modelling and biophysical analysis indicate that the receptor-binding domain (RBD) of the spike glycoprotein is nearly identical in both SARS-CoV-2 and SARS-CoV; however, the binding affinity between ACE2 and RBD is markedly higher for SARS-CoV-2 (Li, 2016; Gui et al., 2017). The TMPRSS2 protease facilitates the receptor binding triggered by the viral spike protein (Hoffmann et al., 2020). The spike protein attaches to the ACE2 extracellular domain, resulting in the endocytosis of the complex via clathrin. (Hoffmann et al., 2020; Turner et al., 2004; Chen et al., 2020).

Surprisingly, individuals with hypertension or coronary artery disease, as well as those with diabetes or other concomitant diseases, had a better outcome (Buhl et al., 2014; Svenningsen et al., 2017; Zheng et al., 2016). Viruses enter the host cell and release viral RNA, which is subsequently replicated using the host cell's machinery to make infectious virion, which is finally discharged by exocytosis. Furthermore, SARS-CoV-2 impacts ACE2 expression and presentation in addition to creating infectious virion through its replication and infection mechanisms. Internalization of receptors reduces the availability of these receptors for cell surface binding. Angiotensin II (ACE2) is a protein that degrades angiotensin I into angiotensin (1-7) peptides, resulting in reduced blood pressure and vasodilation. The absence of antagonism between ACE/angiotensin II and ACE2 is disrupted by ACE2 downregulation; nevertheless, because there is no antagonism in the RAAS, angiotensin II activity is increased (1-7) (Patel et al., 2016). Understanding the biological repercussions of angiotensin II cleavage as a result of ACE2 is required in order to comprehend the relevance of angiotensin II cleavage as a result of ACE2. Angiotensin II is a well-known vasoconstrictor that increases the production of the hormone aldosterone. Interstitial fibrosis, heart dysfunction and hypertrophy, endothelial dysfunction, obesity-related hypertension, elevated inflammation, oxidative stress, and blood coagulation have all been linked to angiotensin II, according to various studies (Zhang et al., 2020; Patel et al., 2016; Turner et al., 2004). Furthermore, angiotensin II increases pulmonary vascular permeability when it binds to AT1R, resulting in increased hydrostatic pressure and, eventually, pulmonary edema (Cha et al., 2018). Under the effect of angiotensin II, Inflammatory lesions in the tracheobronchial tree are increased when ACE2 receptors are downregulated (alveolar wall thickening, inflammatory cell infiltrates, hemorrhage, edema), according to a few experimental investigations of lung damage (Kuba et al., 2005; Hung et al., 2016; Lin et al., 2018).

The relevance of RAAS activation in COVID-19 as a cause of pulmonary edema is yet unknown (Alifano et al., 2020). To determine if the downregulation of ACE2 is a result of COVID-19 infection, a number of clinical findings are required. According to some research, enhanced ACE2 activity may provide COVID-19 protection through anti-inflammatory actions associated with activation of the ACE2/Angiotensin 1-7/Mas axis, which may contribute to improved lung function (Brojakowska et al., 2020).

As a result, in COVID-19, the advantages of ACE inhibitors or ARBs may exceed the dangers (Brojakowska et al., 2020; Ocaranza et al., 2020). Despite this, due to variances in population, ethnicity, and race, the results of anti-hypertensive medication in COVID-19 patients have not been conclusive in recent research. The goal of this study was to see how different antihypertensive medicines affected the blood level of angiotensin-converting enzyme-2 in COVID-19 patients with hypertension who were badly infected.

2. Materials and Methods

Study design

This is a case-control study conducted at the Department of Chemistry and Biochemistry, College of Medicine, Al-Nahrain University. The Ethical Committee of Al-Nahrain University's College of Medicine authorised the study process. Fifty Iraqi patients

with severe COVID-19 infections confirmed by PCR were hospitalised at Al-Yarmouk Hospital and Dar Al Salam Field Hospital 1. Blood samples were collected from all patients following their consent, immediately upon hospitalisation and prior to the administration of any medication. The study was conducted from December 1, 2022, to March 9, 2022. All participants are over 18 and under 80 years of age.

The patients were divided into two groups:

1. Group I: n=25 severe COVID-19 patients with hypertension administered to the hospital that are taking stable dose of current anti-hypertensive medications for at least 4 weeks before their entry to the study.
2. Group Ⅱ: n=25 severe COVID-19 patients without hypertension (as control group) administered to the hospital.

Exclusion criteria:

COVID-19 patients that have other diseases prior to contracting the virus: liver disease, renal failure, cancer.

Blood sample collection and storage:

Approximately 5ml of venous blood samples were collected from all subjects. The blood was allowed to coagulate at room temperature for 15 minutes, after which serum was separated using centrifugation at 3000 rpm for 10 minutes. The serum Human ACE2 measurement was conducted using the Elisa Human Reader obtained from Elabscience Company, USA. Additional tests conducted are C-reactive protein (CRP), ferritin, total lactate dehydrogenase (LDH), and D-dimer assays.

Statistical Analysis

All statistical analyses were conducted utilising SPSS software version 25.0 (SPSS, Chicago). Continuous data underwent a normality assessment using the Shapiro-Wilk test. Data exhibiting a normal distribution were expressed as mean±SD and analysed using either the Student's t-test (for comparisons between two groups) or analysis of variance (ANOVA) followed by least significant difference (LSD) for post hoc pairwise comparisons (for more than two groups). Non-normally distributed data were presented as median and range and analysed using the Mann-Whitney U test (for two groups) or the Kruskal-Wallis test (for more than two groups). Categorical variables were presented as counts and percentages and analysed using the Chi-square test. A p-value below 0.05 was deemed to signify a statistically significant difference.

3. Results

Hypertensive and non-hypertensive patients had a comparable age (59.12±9.62 years and 62.44±10.96 years, respectively) with no significant difference. Males made up the bulk of the patients (64%) in both groups with no significant difference. The concentration of inflammatory parameters and ACE2 were found to be non-normally distributed. Thus, they were expressed as median and range, and analyzed with Mann Whitney U test. The median concentration of ACE2 in hypertensive patients was 3.22 ng/ml (range 1.34-6.89 ng/ml) compared with 0.89 ng/ml (range 0.22-1.35 ng/ml) in non-hypertensive group, with a highly significant difference. Furthermore, hypertensive patients had significantly higher concentration of D-dimer (median= 0.63μg/ml, range= 0.18-9.8 μg/ml) than non-hypertensive patients (median= 0.4 μg/ml, range= 0.16-6.6 μg/ml). Although LDH, CRP and ferritin concentrations were higher in hypertensive than non-hypertensive patients, the differences were non-significant (Table 1).

Table 1: The association of hypertension with COVID-19 Inflammatory parameters in severe cases

Variables	Without hypertension (n=25)	With hypertension (n=25)	p-value

Age, years			
Mean± SD	62.44±10.96	59.12±9.62	0.261↓
Range	39-79	36-73	
Gender			
Male	16(64%)	16(64%)	1.00‡
Female	9(36%)	9(36%)	
ACE2, ng/ml			
Median	0.89	3.22	**<0.001⁑**
Range	0.22-1.35	1.34-6.89	
D-dimer, µg/ml			
Median	0.4	0.63	**0.040⁑**
Range	0.16-6.6	0.18-9.8	
LDH, U/L			
Median	395	548.2	0.093⁑
Range	129.8-950	242-1478.7	
CRP, mg/L			
Median	78.3	87.81	0.214⁑
Range	23-155.34	57.7-155	
Ferritin, ng/ml			
Median	655.34	1200	0.165⁑
Range	45.4-3897.32	181.1-3306	

P-value: 0.05 represents significant difference and >0.001 highly significant difference.

Student t test, ‡Chi square, ⁑Mann Whitney U test

In this study serum concentration of ACE2 was higher in patients on ACE inhibitors (median= 4.85 ng/ml, range= 3.22-6.89 ng/ml) than either those ARBs (median= 2.56 ng/ml, range= 2.27-4.34 ng/ml) or those on Ca-channel blockers (median= 2.43 ng/ml, range= 1.34-4.39 ng/ml) with significant differences. It was also observed that patients on ARBs displayed the lowest concentration of D-dimer, (Table 2).

Table (2): Association of antihypertensive drug with COVID-19 inflammatory parameters in severe cases

Variables	ACE inhibitors (n=7)	ARBs (n=6)	Ca-channel blockers (n=6)	Beta-blockers (n=6)	p-value
Age, years					
Mean± SD	61.29±15.55	61.67±8.91	64.5±12.14	62.5±7.15	0.962*
Range	39-76	51-78	51-79	50-72	
Gender					
Male	7(100%)	2(33.33%)	4(66.67%)	3(50%)	0.072‡
Female	0(0%)	4(66.67%)	2(33.33%)	3(50%)	
ACE2, ng/ml					
Median	4.85[a]	2.56[b]	2.43[b]	3.02[ab]	**0.022****
Range	3.22-6.89	2.27-4.34	1.34-4.29	1.55-4.15	
D-dimer, µg/ml					
Median	0.62	0.31	1.22	1.35	0.519**
Range	0.23-7.7	0.18-7.6	0.38-2.16	0.3-9.8	
LDH, U/L					
Median	490	495	527.5	696.6	0.625**
Range	278-738.9	242-698	387-1478.7	273-1308	
CRP, mg/L					
Median	88.65	80.7	83.8	79.7	0.925**

Range	65.3-123.77	63.1-144.2	57.7-123.5	65.4-155	
Ferritin, ng/ml					
Median	425.9	1880.85	1580	911.93	0.162**
Range	219.06-2444.71	477.8-3306	1176-1962	181.1-2745.6	

4. Discussion

In this study there were no significant differences in the routine laboratory findings (CRP, Ferritin and LDH) between severely affected COVID-19 patients with or without hypertension; even the significant difference of D-dimer was small between the two groups. This may indicate that the severity of the disease in both groups wasn't affected by the level of ACE2 enzyme or by the antihypertensive drugs taken by patients with hypertension prior to the infection. Another study found that anti-hypertensive drugs didn't affect the prognosis in patients with COVID-19, but anti-inflammatory and immune therapies in addition to chronic antihypertensive therapy, could prevent a worse prognosis, and also improve the clinical outcomes in patients with hypertension with COVID-19 infection (Sardu et al., 2020). In this study the level of serum ACE2 enzyme in patients taking ACE inhibitors was significantly higher than the hypertensive patients taking ARBs or Ca-channel blockers or beta-blockers. Previous studies did report that the renin-angiotensin-aldosterone system (RAAS) inhibitors increased expression of ACE2 in rat models and human cells in vitro (Kreutz et al., 2020; Igase et al., 2008; Ferrario et al., 2005). Therefore, concerns were raised about the use of ACEIs/ARBs, which have the potential to boost COVID-19 infectivity. A study by Galán and Jiménez-Altayó, 2020, showed that ACE2 is the SARS-CoV-2 receptor, a functional variation with enhanced gene expression linked to a larger number of membrane-bound viral binding sites, making carriers more vulnerable to infection (Galán and Jiménez-Altayó., 2020).

Nonetheless, several research corroborated the beneficial effects of ACE inhibitors and angiotensin receptor blockers. Numerous studies have demonstrated the advantageous impact of ACE2 in mitigating lung injury, mediated by the activation of the ACE2/Ang 1-7/MAS pathway, which counteracts the harmful effects of oxidative stress and inflammatory reactions. (Kreutz et al., 2020; Danser et al., 2020; Kuba et al., 2005). The upregulation of ACE2 expression by ACE inhibitors or angiotensin receptor blockers may not be detrimental; rather, it could be advantageous. This study corroborates numerous investigations that identified no correlation between ACEIs/ARBs and clinical outcomes or adverse events, hence suggesting no justification for the cessation of ACEIs/ARBs during the COVID-19 pandemic. (Sardu et al., 2020; Wang et al., 2020; An et al., 2021).

5. Conclusion

This study showed that the use of antihypertensive drugs (ACE inhibitors or ARBs or Ca-channel blockers) prior to the COVID-19 infection is an infection caused by the virus COVID-19 was not associated with the severity of disease and therefore, should not be discontinued during the course of infection. As for the use of ACE inhibitors or ARBs in addition to standard medication for COVID-19 may or may not help in preventing worse prognosis in patients with severe COVID-19 infection and further investigation of their benefits during the course of the pandemic still needs extensive research.

REFERENCES

[1] ALIFANO, M., ALIFANO, P., FORGEZ, P. & IANNELLI, A. 2020. Renin-angiotensin system at the heart of COVID-19 pandemic. *Biochimie,* 174**,** 30-33.

[2] AN, J., ZHOU, H., WEI, R., LUONG, T. Q., GOULD, M. K., MEFFORD, M. T., HARRISON, T. N., CREEKMUR, B., LEE, M.-S. & SIM, J. J. 2021. COVID-19 morbidity and mortality associated with angiotensin-converting enzyme

inhibitors or angiotensin receptor blockers use among 14,129 patients with hypertension from a US integrated healthcare system. *International Journal of Cardiology Hypertension*, 100088. https://doi.org/10.1016/j.ijchy.2021.100088

[3] BROJAKOWSKA, A., NARULA, J., SHIMONY, R. & BANDER, J. 2020. Clinical implications of SARS-CoV-2 interaction with renin angiotensin system: JACC review topic of the week. *Journal of the American College of Cardiology,* 75**,** 3085-3095.

[4] BUHL, K. B., OXLUND, C. S., FRIIS, U. G., SVENNINGSEN, P., BISTRUP, C., JACOBSEN, I. A. & JENSEN, B. L. 2014. Plasmin in urine from patients with type 2 diabetes and treatment-resistant hypertension activates ENaC in vitro. *Journal of hypertension,* 32**,** 1672-1677.

[5] CHA, S. A., PARK, B. M. & KIM, S. H. 2018. Angiotensin-(1-9) ameliorates pulmonary arterial hypertension via angiotensin type II receptor. *The Korean Journal of Physiology & Pharmacology,* 22**,** 447-456.

[6] CHEN, Y., GUO, Y., PAN, Y. & ZHAO, Z. J. 2020. Structure analysis of the receptor binding of 2019-nCoV. *Biochemical and biophysical research communications,* 525**,** 135-140.

[7] DANSER, A. J., EPSTEIN, M. & BATLLE, D. 2020. Renin-angiotensin system blockers and the COVID-19 pandemic: at present there is no evidence to abandon renin-angiotensin system blockers. *Hypertension,* 75**,** 1382-1385.

[8] FERRARIO, C. M., JESSUP, J., CHAPPELL, M. C., AVERILL, D. B., BROSNIHAN, K. B., TALLANT, E. A., DIZ, D. I. & GALLAGHER, P. E. 2005. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. *Circulation,* 111**,** 2605-2610.

[9] GALÁN, M. & JIMÉNEZ-ALTAYÓ, F. 2020. Small resistance artery disease and ACE2 in hypertension: a new paradigm in the context of COVID-19. *Frontiers in Cardiovascular Medicine,* 7.

[10] GUI, M., SONG, W., ZHOU, H., XU, J., CHEN, S., XIANG, Y. & WANG, X. 2017. Cryo-electron microscopy structures of the SARS-CoV spike glycoprotein reveal a prerequisite conformational state for receptor binding. *Cell research,* 27**,** 119-129.

[11] HOFFMANN, M., KLEINE-WEBER, H., SCHROEDER, S., KRÜGER, N., HERRLER, T., ERICHSEN, S., SCHIERGENS, T. S., HERRLER, G., WU, N.-H. & NITSCHE, A. 2020. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *cell,* 181**,** 271-280. e8.

[12] HUNG, Y.-H., HSIEH, W.-Y., HSIEH, J.-S., LIU, C., TSAI, C.-H., LU, L.-C., HUANG, C.-Y., WU, C.-L. & LIN, C.-S. 2016. Alternative roles of STAT3 and MAPK signaling pathways in the MMPs activation and progression of lung injury induced by cigarette smoke exposure in ACE2 knockout mice. *International journal of biological sciences,* 12**,** 454.

[13] IGASE, M., KOHARA, K., NAGAI, T., MIKI, T. & FERRARIO, C. M. 2008. Increased expression of angiotensin converting enzyme 2 in conjunction with reduction of neointima by angiotensin II type 1 receptor blockade. *Hypertension Research,* 31**,** 553-559.

[14] KREUTZ, R., ALGHARABLY, E. A. E.-H., AZIZI, M., DOBROWOLSKI, P., GUZIK, T., JANUSZEWICZ, A., PERSU, A., PREJBISZ, A., RIEMER, T. G. & WANG, J.-G. 2020. Hypertension, the renin–angiotensin system, and the risk of lower respiratory tract infections and lung injury: implications for COVID-19: European Society of Hypertension COVID-19 Task Force Review of Evidence. *Cardiovascular research,* 116**,** 1688-1699.

[15] KUBA, K., IMAI, Y., RAO, S., GAO, H., GUO, F., GUAN, B., HUAN, Y., YANG, P., ZHANG, Y. & DENG, W. 2005. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus–induced lung injury. *Nature medicine,* 11**,** 875-879.

[16] LI, F. 2016. Structure, function, and evolution of coronavirus spike proteins. *Annual review of virology,* 3**,** 237-261.

[17] LIN, C.-I., TSAI, C.-H., SUN, Y.-L., HSIEH, W.-Y., LIN, Y.-C., CHEN, C.-Y. & LIN, C.-S. 2018. Instillation of particulate matter 2.5 induced acute lung injury and attenuated the injury recovery in ACE2 knockout mice. *International journal of biological sciences,* 14**,** 253.

[18] OCARANZA, M. P., RIQUELME, J. A., GARCÍA, L., JALIL, J. E., CHIONG, M., SANTOS, R. A. & LAVANDERO, S. 2020. Counter-regulatory renin–angiotensin system in cardiovascular disease. *Nature Reviews Cardiology,* 17**,** 116-129.

[19] PATEL, V. B., ZHONG, J.-C., GRANT, M. B. & OUDIT, G. Y. 2016. Role of the ACE2/angiotensin 1–7 axis of the renin–angiotensin system in heart failure. *Circulation research,* 118**,** 1313-1326.

[20] SARDU, C., MAGGI, P., MESSINA, V., IULIANO, P., SARDU, A., IOVINELLA, V., PAOLISSO, G. & MARFELLA, R. 2020. Could anti-hypertensive drug therapy affect the clinical prognosis of hypertensive patients with COVID-19 infection? Data from centers of southern Italy. *Journal of the American Heart Association,* 9**,** e016948.

[21] SVENNINGSEN, P., HINRICHS, G. R., ZACHAR, R., YDEGAARD, R. & JENSEN, B. L. 2017. Physiology and pathophysiology of the plasminogen system in the kidney. *Pflügers Archiv-European Journal of Physiology,* 469**,** 1415-1423.

[22] TURNER, A. J., HISCOX, J. A. & HOOPER, N. M. 2004. ACE2: from vasopeptidase to SARS virus receptor. *Trends in pharmacological sciences,* 25**,** 291-294.

[23] WANG, H., LI, X., LI, T., ZHANG, S., WANG, L., WU, X. & LIU, J. 2020a. The genetic sequence, origin, and diagnosis of SARS-CoV-2. *European Journal of Clinical Microbiology & Infectious Diseases***,** 1-7.

[24] WANG, Z., ZHANG, D., WANG, S., JIN, Y., HUAN, J., WU, Y., XIA, C., LI, Z., QI, X. & ZHANG, D. 2020b. A retrospective study from 2 centers in China on the effects of continued use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers in patients with hypertension and COVID-19. *Medical Science Monitor: International Medical Journal of Experimental and Clinical Research,* 26**,** e926651-1.

[25] ZHANG, H., PENNINGER, J. M., LI, Y., ZHONG, N. & SLUTSKY, A. S. 2020. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. *Intensive care medicine,* 46**,** 586-590.

[26] ZHENG, H., LIU, X., SHARMA, N. M., LI, Y., PLIQUETT, R. U. & PATEL, K. P. 2016. Urinary proteolytic activation of renal epithelial Na+ channels in chronic heart failure. *Hypertension,* 67**,** 197-205.