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Research Article

Long-term RAAS Dysregulation in Post-COVID-19 Cardiovascular Complications: AT-II and ACE2 Imbalance

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I N F O

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A B S T R A C T

Introduction: Severe acute respiratory syndrome coronavirus 2, the causative agent of coronavirus disease 2019 (COVID-19), is associated with various cardiovascular complications.

Aim: This observational study investigated long-term changes in angiotensin system components, specifically angiotensin II (AT-II) and angiotensin-converting enzyme 2 (ACE2), in patients with and without cardiovascular complications following COVID-19 infection.

Methods: The study included 122 adults aged 22-72 years, divided into a control group (mild COVID-19 without pneumonia or heart issues), group I (COVID-19 with lung involvement but no heart complications), and group II (COVID-19 with lung damage and heart complications). Blood samples were obtained one year after acute COVID-19, and serum concentrations of AT-II and ACE2 activity were measured using enzyme-linked immunosorbent assay kits.

Results: The results showed a significant increase in AT-II levels and a decrease in ACE2 activity in Group II compared to the control and Group I. In group II, 73% of patients had elevated AT-II levels and 77% showed reduced ACE2 activity, indicating a persistent imbalance between the regulatory and counterregulatory components of the angiotensin system.

Conclusion: This study showed that increased AT-II levels and decreased ACE2 activity may contribute to cardiovascular problems during post-acute COVID-19 infection.

Keywords: COVID-19, cardiovascular complications, angiotensin-converting enzyme 2, renin-angiotensin-aldosterone system, angiotensin II

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative agent of coronavirus disease 2019 (COVID-19), a transmissible disease that predominantly affects the respiratory system and may result in severe complications, such as kidney failure.[1–4]

It is now well established that one of the primary complications arising from COVID-19 is damage to the cardiovascular system, particularly in elderly patients.[5] These complications encompass a broad spectrum of cardiovascular and thrombotic issues associated with coronavirus infections.[6] Cardiovascular syndrome can manifest in various forms, including different types of arrhythmias, such as atrial fibrillation, ventricular tachycardia, and fibrillation, as well as myocardial complications, pericarditis, and both arterial and venous thrombotic conditions, such as acute coronary syndrome and deep vein thrombosis. Additionally, pulmonary hypertension has been observed.

Cardiac issues can be a direct result of COVID-19 or may arise as a consequence of lung damage.[7] Cardiovascular symptoms can manifest at any stage during hospitalisation and even more than a year after the acute phase of the illness has ended. Cardiovascular complications often emerge after the patient's respiratory condition stabilises and improves.[7]

Currently, the reasons behind the cardiac issues linked to COVID-19 and their impact on the cardiovascular system in certain patients remain unclear. A potential mechanism of harm could be linked to the heightened expression of angiotensin-converting ensyme type 2 (ACE2) in the heart and vascular endothelium.[8] ACE2 plays a crucial role in the renin-angiotensin-aldosterone system (RAAS), which is implicated in the development of cardiovascular diseases. ACE2 is a type transmembrane protein found in the lungs, heart, kidneys, vascular endothelium, liver, testicles, and intestines, and it also exists in a free form in the bloodstream.[9-11]

The physiological function of ACE involves converting Angiotensin II (AT-II) angiotensin 1 to inactive peptide Angiotensin-(1-9) [Ang-(1-9)], which transforms into Ang-(1-7) via ACE, and breaking down AT-II into Ang-(1-7), which interacts with Mas receptors. Ang-(1-7) provides protective effects on blood vessels and the heart, including antiproliferative, anti-inflammatory, and natriuretic benefits. By degrading AT-II, ACE2 reduces its adverse effects, such as vasoconstriction, cytokine-like activity, sodium retention, and fibrosis.[12-17]

Research on the angiotensin system in COVID-19 remains scarce, highlighting the need for this study. This study aimed to explore the pathophysiological role of the angiotensin system in cardiac complications of COVID-19, particularly in the later stages after the acute phase.

Methods

This observational study involved 122 adults aged 22-72 years who were diagnosed with COVID-19 during the May 2022 to April 2024. This study assessed long-term changes in angiotensin system components in patients with and without cardiovascular complications following COVID-19 infection. This study was conducted in accordance with the Declaration of Helsinki. The Bioethics Committee of the International Higher School of Medicine granted ethical approval (protocol no. 21, dated April 18, 2024). Data confidentiality was maintained, and personal identifiers were removed before the analysis.

Participants were divided into control and two clinical groups: Control group (n = 28): Individuals with mild COVID-19 treated as outpatients without pneumonia or heart issues. Group I (n = 42): Patients with COVID-19 with lung involvement but no heart complications. Group II (n = 52): Patients with lung damage and heart complications after COVID-19.

In Group II, cardiovascular issues included myocarditis, arrhythmias, arterial hypertension, pericarditis, and pulmonary hypertension. COVID-19 and its complications were confirmed using reverse transcriptase polymerase chain reaction, chest computed tomography, echocardiography, and electrocardiography.

Individuals were included if they had confirmed COVID-19 via reverse transcriptase polymerase chain reaction, were age 22-72 years, and had recovered from acute COVID-19 at least a year before recruitment. The exclusion criteria were as follows: pre-existing chronic cardiovascular diseases unrelated to COVID-19; use of medications affecting the renin-angiotensin-aldosterone system (such as Angiotensin-Converting Enzyme inhibitors or Angiotensin II Receptor Blockers) during the study; chronic kidney or liver disease; and any active infection, autoimmune disorder, or cancer at sampling

Blood samples were obtained from the participants one year after acute COVID-19. The serum concentrations of AT-II and ACE2 activity were measured using enzyme-linked immunosorbent assay (ELISA) kits, specifically the Human Angiotensin-converting enzyme 2, ACE2 ELISA Kit (Cusabio, Texas, United States). All procedures were performed according to the manufacturer's instructions. Blood samples were handled under standard biosafety conditions, and the serum was stored at suitable temperatures until analysis.

Biochemical tests were performed in a certified clinical laboratory, following standard procedures. The ELISA kits were validated using internal controls and duplicates for accuracy. Both inter- and intra-assay variation coefficients

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were maintained below 10%. Calibration curves were created for each session, and the results outside the expected range were re-examined.

Statistical analysis of the biochemical assay data used descriptive and inferential techniques. For each group, data are presented as mean (M) ± standard deviation (m). Parametric tests were employed to assess the significance of the differences in serum AT II and ACE2 levels between the groups. Analysis was performed using STATISTICA 6.0 software (StatSoft Inc., USA), with significance set at $P < 0.05$.

The results are expressed as mean (M) ± standard deviation (m), and intergroup differences are highlighted based on significance levels (e.g., P_{2-1}, P_{3-1}, and P_{3-2} comparisons). The range of fluctuations compared to the control values was examined to identify patients with outlier values in each group.

Results

In the entire group of patients, 57% were men and 43% were women, with an average age of 43.4 ± 11.5 years. A comparative study of serum angiotensin markers across three groups (control, group I [with pulmonary involvement but no cardiovascular complications], and group II [with both pulmonary involvement and cardiovascular complications]) showed notable differences in essential components 12 months or more after COVID-19 recovery.

In group I, patients showed a rise in serum AT-II levels (15.5 ± 1.32 pg/ml) compared to controls (12.26 ± 1.04 pg/ml); however, this difference was not statistically significant ($P > 0.05$). Group II showed a notable increase in AT-II levels (21.4 ± 2.6 pg/ml) compared to the control group ($P < 0.01$) and group I ($P < 0.05$), suggesting activation of the pressor component of the RAAS in patients with cardiovascular issues post-COVID-19 (Table 1). Analysis showed that eight patients (19%) in group I had AT-II levels outside the control group confidence interval. In group II, this percentage reached 73% (38 patients), highlighting AT2 level dysregulation in patients with cardiac complications.

The examination of serum ACE2 activity revealed different patterns. Group I showed ACE2 levels (42.4 ± 4.5 pg/ml) similar to the control group (38.8 ± 3.6 pg/ml), with no significant difference ($P > 0.05$). Group II showed decreased ACE2 activity (28.4 ± 3.1 pg/ml) compared to both the control and group I ($P < 0.05$ for both), indicating impairment in the vasoprotective function of the angiotensin system (Table 1). Within groups, 7 (16.6%) patients in group I had ACE2 levels outside the control range, while 40 patients (77%) in group II showed this pattern, reinforcing significant dysregulation in patients with cardiovascular involvement.

The results indicate a persistent imbalance between the regulatory (AT-II) and counterregulatory (ACE2) components of the angiotensin system in individuals recovering from COVID-19, particularly those with cardiovascular issues. The increase in AT-II levels and decrease in ACE2 activity suggest a continuous proinflammatory, profibrotic, and vasoconstrictive condition that may contribute to cardiovascular problems during the post-acute phase. Table 1 summarises the findings, presenting the average values, standard errors, and statistical significance of group comparisons for the AT-II and ACE2 metrics.

The percentage of patients with measurements outside the normal physiological range differed between the groups. In Group II, 73% of the participants had elevated AT-II levels, indicating a sustained pressor response. In contrast, only 19% of patients in Group I exhibited similar abnormalities. For ACE2 activity, 77% of Group II patients showed reduced levels compared to controls, suggesting a diminished vasoprotective capacity. This trend was less prevalent in Group I (16.6%), where ACE2 levels remained within the normal range. These results highlight angiotensin system dysregulation after recovery in patients with cardiovascular involvement, potentially indicating a subgroup that requires extended cardiovascular monitoring.

Table 1.Serum levels of AT-II and ACE2 activity in in the examined groups of patients

S No.	Groups	Statistical indicators	Indicators, pg/ml	
			AT-II	ACE2
1.	Control group (n = 28)	M ± m	12.26 ± 1.04	38.8 ± 3.6
2.	Group I (n = 42)	M ± m P_{2-1}	15.5 ± 1.32 >0.05	42.4 ± 4.5 >0.05
3.	Group II (n = 52)	M ± m P_{3-1} P_{3-2}	21.4 ± 2.6 <0.01 <0.05*	28.4 ± 3.1 <0.05* <0.05*

Values are expressed as the M ± m = Mean ± Standard deviation. ACE2 – Angiotensin-Converting Enzyme 2, AT-II – Angiotensin II. P_{2-1} – Comparison between group I and control Group, P_{3-1} – Comparison between group II and control group, P_{3-2} – Comparison between group II and group I. *P <0.05.

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Discussion

This study examined long-term changes in key elements of the RAAS, specifically AT-II and ACE2, in patients who contracted COVID-19, focusing on those with cardiovascular issues. The results showed a notable imbalance in the RAAS within this group, marked by increased AT-II levels and decreased ACE2 activity. These changes likely contribute to the persistent cardiovascular problems observed in post-acute COVID-19.

COVID-19 is a systemic illness that affects multiple body systems beyond the respiratory tract. Cardiovascular issues, including myocarditis, arrhythmias, thromboembolism, and heart failure, have been associated with viral impact, immune system damage, and RAAS disruption.[18-20] This study found that patients with cardiovascular complications had higher AT-II levels than those in the control group and pulmonary-only cases, aligning with findings suggesting increased RAAS activation in severe COVID-19.[21]

ACE2 acts as both the entry point for SARS-CoV-2 and a regulator of the RAAS, highlighting its role in COVID-19 pathophysiology.[22] ACE2 typically breaks down AT-II into Ang-(1-7), which mitigates the vasoconstrictive, proinflammatory, and profibrotic effects of AT-II [6,7].[23,24] In patients with Group II, reduced ACE2 activity disrupts this equilibrium, leading to increased AT-II effects. This imbalance contributes to the inflammatory environment and vascular changes observed in post-COVID cardiac issues.[25]

Our findings align with those of previous studies showing reduced serum ACE2 activity in individuals with cardiovascular disease after COVID-19.[26] We detected an inverse relationship between AT-II and ACE2 levels in Group II patients, supporting the theory that RAAS remains abnormally active over the long term. Although this study did not evaluate other indicators of endothelial dysfunction or fibrosis, increased AT-II levels have been linked to fibrosis, oxidative stress, and apoptosis in cardiovascular tissues.[27]

Research indicates that reduced ACE2 after viral entry might worsen the RAAS imbalance, especially in those with hypertension, obesity, or diabetes.[28,29] Although we excluded patients with known chronic cardiovascular diseases, undiagnosed conditions may have influenced these changes. Additionally, the findings suggest that RAAS alterations could persist for months post-viral clearance, particularly in "long COVID" or post-acute SARS-CoV-2 infection.[11]

The high prevalence of abnormal RAAS markers in our Group II cohort, with 73% for AT-II and 77% for ACE2, suggests that evaluating these biomarkers could help identify individuals at risk for enduring cardiovascular complications. Tracking RAAS components may provide insights into ongoing pathophysiological changes and help direct treatment strategies, such as RAAS inhibitors or anti-fibrotic medications.[30]

An inverse relationship was found between serum AT-II levels and ACE2 activity in patients with cardiovascular issues after COVID-19, indicating RAAS disruption. Group II patients showed higher AT-II levels and lower ACE2 activity. This inverse correlation suggests that decreased ACE2 levels may lead to AT-II accumulation, promoting vasoconstriction, inflammation, and fibrosis. Although this observational study lacked formal statistical correlation analysis, the biological trend matches studies showing that SARS-CoV-2 entry reduces membrane-bound ACE2, disrupting Ang-(1-7)-Mas signaling.[21,22] These findings align with Alymkulov et al. high-altitude study, where ACE2 deficiency led to adverse outcomes in untreated hypertensive COVID-19 patients.[31] The persistent dysregulation of ACE2/AT-II suggests that RAAS imbalance contributes to cardiovascular symptoms in patients with long COVID, warranting future longitudinal studies to clarify its prognostic significance.

In Group II, a reverse correlation was observed between serum AT-II levels and ACE2 activity. Patients with high AT-II concentrations often show the lowest ACE2 activity, supporting the theory of a disrupted renin-angiotensin system in post-COVID-19 cardiovascular conditions. Although formal correlation analysis was not conducted, the findings suggest a biological imbalance that could lead to vascular remodeling, endothelial dysfunction, and cardiovascular issues. This dysregulation provides a mechanistic rationale for ongoing symptoms, such as arrhythmias, hypertension, and myocarditis, in patients with long COVID and cardiovascular complications.

This study was observational rather than interventional, limiting our ability to draw causal links between angiotensin system changes and cardiovascular issues after COVID-19. Serum AT-II and ACE2 levels were measured once a year infectionection. Longitudinal data would better show how these biomarkers relate to ongoing or resolved symptoms. The lack of baseline biomarker levels before COVID-19 infection complicates the determination of whether the observed dysregulation is new or an intensification of existing conditions. Despite strict inclusion and exclusion criteria, factors such as undiagnosed hypertension, recovery time differences, and treatment variations during acute COVID-19 could have affected the results. The study's specific geographical setting (Kyrgyz Republic) may limit the applicability of the findings to wider populations.

Conclusions

This study showed a long-term disruption in the RAAS among patients with cardiovascular complications after COVID-19. The results indicate that high serum AT-II and

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decreased ACE2 activity persist for more than a year after infection, especially in patients with post-COVID heart issues. This imbalance implies ongoing proinflammatory, profibrotic, and vasoconstrictive processes that may drive the emergence and persistence of cardiovascular symptoms.

The inverse correlation between AT-II and ACE2 levels indicates a disrupted counter-regulatory mechanism in the RAAS. This imbalance may explain post-acute cardiovascular issues, such as myocarditis, hypertension, and arrhythmias, in patients with long COVID. Measuring serum AT-II and ACE2 levels may help identify patients at risk of long-term cardiovascular problems, aiding follow-up strategies and treatment. Future longitudinal research is needed to establish causal links, assess the prognostic significance of these biomarkers, and investigate RAAS-modulating treatments in this group.

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