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Research article

Investigating the relationship between COVID-19 and total oxidative stress and antioxidant capacity in individuals

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Abstract

Free oxygen radicals are effective in the development and progression of viral infections. The aim of this study was to evaluate the levels of oxidative stress in individuals who have been diagnosed with COVID-19, a viral disease nowadays. The study was carried out between March 2021 and June 2021. Blood samples of 50 patients who applied to Medipol University Faculty of Medicine with suspected COVID-19 infection, whose clinical and molecular diagnoses were corrected and were taken for routine evaluations, were included in this study. In the healthy group, 50 serum samples taken before the COVID-19 pandemic were used. Total antioxidant status (TAS) and total oxidant status (TOS) levels were measured, and the data collected were then statistically compared. The TAS level in the COVID-19 group (1.470±0.269) was lower than the healthy group TAS level (1.491±0.286), but it was not statistically significant ($p>0.05$). The TOS level in COVID-19 group was 13.962 (3.02±36.35) while it was low as 7.925 (1.19±15.03) in the healthy group. The high TOS value in the COVID-19 group was found to be statistically significant compared to the healthy group ($p<0.05$). Oxidative stress index (OSI) levels, calculated from TOS/TAS, in the COVID-19 group were 9.356 (1.80±26.54) while they were 5.388 (0.98±10.93) in the healthy group. The levels of OSI were found to be significantly higher in the COVID-19 group when compared to the healthy group ($p<0.05$). The presence of oxidative stress markers in the COVID-19 patients plays an important role in the pathological examination of cell damage. This approach may also pave the way for new therapeutic approaches.

Keywords: *Antioxidant; cell damage; COVID-19; oxidative stress*

1. Introduction

Coronaviruses (CoVs) are enveloped single-stranded RNA viruses. CoVs can lead to health problems ranging from the ordinary cold to fatal acute respiratory illnesses. After the COVID-19 disease was first discovered in China, there have been reports of it spreading all over the world with an increasing number of patients. The World Health Organization (WHO) proclaimed a COVID-19 infection pandemic because of this outbreak, which resulted in thousands of fatalities (Genc, 2020; Kocyigit, 2020; Sharma et al., 2021).

The clinical spectrum of COVID-19 infection ranges from moderate respiratory tract illness to severe viral pneumonia and even death (Kocyigit, 2020). The pathogenesis of COVID-19 infection can be impacted by various factors, such as heightened levels of inflammation, increased oxidative stress, and disruption of immune response regulation. The presence of these factors can potentially induce the excessive release of pro-inflammatory cytokines, which can result in severe complications like acute respiratory distress syndrome (ARDS), shock, and even mortality. This phenomenon, commonly referred to as a "cytokine storm", can have significant

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consequences. The excessive and uncontrolled release of cytokines, which can happen in response to a variety of conditions such as infections, autoimmune diseases, and cancer, results in the deadly state known as the cytokine storm. Uncontrolled immune system activation can result in the production of proinflammatory cytokines, which can cause damage to tissues and organs throughout the body. This can result in a range of symptoms, from fever and fatigue to respiratory failure and multiple organ dysfunction syndrome (MODS). The severity of the cytokine storm depends on many factors, including the type and duration of the stimulus, as well as individual differences in immune function. Supportive care and immunomodulatory medicines targeted at reducing inflammation and restoring immunological balance are frequently used in the treatment of cytokine storms. Even though there are still many unanswered questions regarding this complicated condition, ongoing research is shedding light on its underlying processes and prospective therapy targets (Delgado-Roche et al., 2020; Qin et al., 2020).

COVID-19 predominantly impacts the lungs as the primary target organ. The virus enters host cells by binding to Angiotensin-converting enzyme 2 (ACE-2) receptors located on the surface of lung alveolar cells. Subsequently, it propagates along the respiratory system, reaching the lungs. Reproducing in host cells, the virus causes severe inflammation and cellular damage (Uras, 2021).

Several studies have shown that some viruses adopt a strategy to modify the redox balance of a cell. In addition, the initiation of oxidative stress triggered by viral infection has been found to play a crucial role in the activation of innate immune responses aimed at eliminating pathogenic microbes (Kim et al., 2013; Narayanan et al., 2014; Cecchini and Cecchini, 2020).

Neutrophil infiltration and severe hypoxemia are seen in the lungs as a result of the cytokine storm caused by the illness. Organ failure and mortality, as well as oxidative stress and cell damage, are brought on by the respiratory burst mechanism, which generates a fast release of free oxygen species (ROS) in response to inflammation (Celik and Kose, 2020). Oxidative stress occurs when there is an imbalance between the processes of oxidation and antioxidation within the organism. Therefore, oxidative stress and the inflammatory response are strongly connected. Aging, some chronic diseases including diabetes mellitus, cancer, hypertension, and some diseases brought on by RNA viruses like CoV are all affected by oxidative stress (Feng et al., 2017).

Individual measurements of oxidant and antioxidant molecules are used to assess oxidative stress and antioxidant capability. However, complete measuring approaches have lately gained popularity (Erel, 2005). Total oxidant levels (TOS) and total antioxidant levels (TAS) are two metrics used to assess the overall state of oxidative stress in the body. These parameters help gauge the balance between oxidants and antioxidants, providing insights into the oxidative stress levels within the organism (Rampelotto et al., 2023).

The overall antioxidant status of the body is ascertained by TAS testing, whereas the general oxidation state is ascertained by TOS measurement. The ratio of TOS to TAS is used to compute the oxidative stress index (OSI), which measures how well the body is balancing its levels of oxidants and antioxidants (Wu et al., 2017).

Scientific studies suggested a link between oxidative stress, and mortality risk of patients infected severe acute respiratory syndrome coronavirus (SARS-CoV). However, more research is needed to explore the potential of oxidant and antioxidant stress parameters in patients with COVID-19 (Derouiche, 2020; Zeliger and Kahaner, 2020).

In order to do this, TAS and TOS parameters and contrasted the levels of TAS and TOS in COVID-19 patients with healthy people were assessed.

2. Materials and methods

2.1. Patients

The current study was conducted from March 2021 to June 2021. In this study, 50 blood samples from patients who applied to Istanbul Medipol University's Faculty of Medicine with the suspicion of COVID-19 infection and whose diagnoses were done by Polymerase Chain Reaction (PCR) tests were used. The patients ranged in age from 10 to 88 years old. Patients who were taking antioxidant medication, were pregnant, or had autoimmune, metabolic, or systemic illnesses were excluded from the study. In addition, the healthy group consisted of 50 serum samples collected prior to the COVID-19 pandemic.

Healthy Group (n=50): Comprised of healthy individuals with negative COVID-19 results.

Patients with positive COVID-19 results consisted of the COVID-19 Group (n=50).

2.2. Procedures

The blood samples were obtained from the patients and subsequently subjected to centrifugation at a speed of 3800 rpm for a duration of 10 minutes. Afterward, samples were stored in 500 μL aliquots at -80°C until the testing time. Then all dissolved at once and studied according to the Erel method (Erel, 2005).

The TOS and TAS levels with RelAssay® Diagnostics kits (Mega Medicine, Gaziantep, Türkiye) were measured based on the colorimetric method. The TOS results were quantified and expressed in terms of μmol H_2O_2 equivalent per liter (H_2O_2 eq/L). The TAS results were presented as mmol/L Trolox equivalent. The percent ratio of TOS to TAS level was accepted as OSI values.

2.3. Statistical analysis

Statistical analyses were performed with IBM SPSS Statistics for Windows, Version 22 package program. For data that followed a normal distribution, Student's t-test was employed, while the Mann-Whitney U test was used for data that deviated from normality. Descriptive statistics were computed, including the mean ± standard deviation and the median values. The values were accepted as statistically significant when $p<0.05$.

2.4. Ethics statement

The Ethics Committee of the School of Medicine at Istanbul Medipol University approved the current study (Date: 27.01.2021, Decision no: 2667). All participants received information about the study, and they all voluntarily signed and date the informed consent form. All participants in the trial, including patients and healthy volunteers, verbally consented after being fully informed. The trial was open to patients who hadn't taken any medication before to blood collection.

3. Results

The COVID-19 group consisted of 22 females and 28 males. There were 19 female and 31 male patients in healthy group. Table 1 presents the demographic data of the groups. In the COVID-19 group, the levels of TAS (1.470±0.269) were observed to be slightly lower compared to the healthy group (1.491±0.286). However, this difference was not found to be statistically significant ($p>0.05$), as depicted in Fig. 1.

Table 1
Demographic data of the groups.

Parameters	Healthy Group	COVID-19 Group	*p* Value
Age (Median)	35 (8-66)	36.5 (10-88)	0.535
Female / Male, n	19/31	22/28	0.544

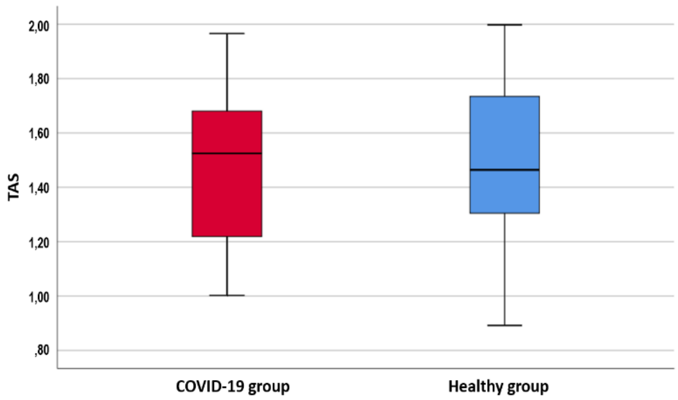

Fig. 1. TAS results.

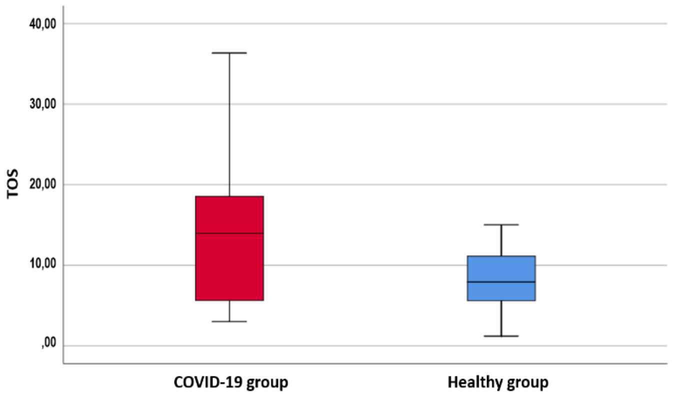

Fig. 2. TOS results.

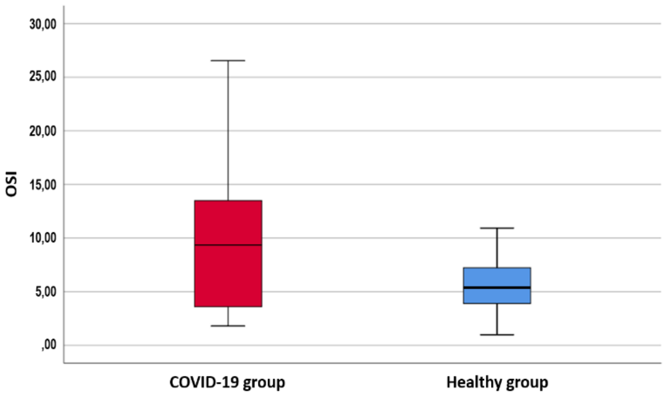

Fig. 3. OSI results.

TOS levels in the COVID-19 group 13.962 (3.02±36.35) were higher than the healthy group 7.925 (1.19±15.03) and statistically significant ($p<0.05$) (Fig. 2). OSI levels in the COVID-19 group were measured as 9.356 (1.80±26.54) while they were measured as 5.388 (0.98±10.93) in the healthy group and this was statistically significant ($p<0.05$) (Fig. 3).

4. Discussion

This study revealed that COVID-19 patients exhibited significantly higher levels of total oxidative stress and oxidative stress index compared to healthy individuals. The total antioxidant capacity levels in the COVID-19 group were slightly lower than those in the healthy group, but the difference was not statistically significant. These findings indicate that COVID-19 induces oxidative stress within the body, potentially contributing to cellular damage and the progression of the disease.

Additionally, the oxidative stress induced by COVID-19 can result in systemic tissue damage, which is likely to hinder the proper functioning of adaptive immunity (Bakadia et al., 2021). In the prior study conducted by Lin et al., it was reported that a viral protease called SARS-CoV 3CLpro was found to boost ROS generation (Lin et al., 2006). According to the authors, the pathophysiology of SARS-COV is significantly influenced by the rise in ROS generation (Delgado-Roche et al., 2020). One of the significant risk variables linked to COVID-19 severity and mortality includes older age, ethnicity, male sex, low socioeconomic position, hyperglycemia, and obesity. Additionally, connected to elevated oxidative stress are all these risk factors. Due to all these factors is related to a number of characteristics observed in oxidative stress and COVID-19 infection (Chernyak et al., 2020).

In the study conducted by Aykac et al. (2021) the researchers measured the TOS levels in children and adult healthy individuals, as well as individuals with COVID-19. They found that the TOS levels were higher in the children and adults with COVID-19 compared to the healthy groups. This suggests that individuals with COVID-19 may experience higher levels of oxidative stress compared to healthy individuals.

Recently, researchers have shown that COVID-19 disrupts mitochondrial homeostasis. This process also causes oxidative damage in COVID-19 patients. Dagli et al. (2022) reported that the OS parameters, TAS, TOS, MDA and PC levels increased in COVID-19 patients. The elevated levels of TOS and OSI detected in patients with COVID-19 underscore the significance of antioxidant therapy as a prospective therapeutic strategy for addressing COVID-19. Antioxidants play a crucial role in neutralizing free radicals and reducing oxidative stress within the body. By counteracting the harmful effects of free radicals, antioxidants help maintain a balance between oxidation and antioxidation, thus mitigating the detrimental impact of oxidative stress. Therefore, the use of antioxidants may help to prevent or alleviate the cell damage caused by the virus. In healthy people, a boost in antioxidant defense balances off the excess ROS generation. Red blood cells peroxide when ROS generation is improperly managed in individuals with defective redox equilibrium (RBC). According to the study by Laforge et al., increased generation of oxidative stress may contribute to alveolar damage, thrombosis, and dysregulation of red blood cells in individuals with COVID-19. Their research suggests that the elevated oxidative stress levels observed in COVID-19 patients could play a role in these pathological processes (Laforge et al., 2020). According to Muhammad et al., COVID-19 patients had low plasma levels of the antioxidant vitamins A, C, and E, but COVID-19 patients had high amounts of malondialdehyde, one of the indicators of oxidative stress. To counteract the damaging effects of free radicals, antioxidant levels are likely to decline in COVID-19 patients (Muhammad et al., 2021).

It is important to remember that ROS generation brought on by viral infection cannot be seen as a single damaging agent. Additionally, ROS is necessary for the phagocytosis of viruses by immune cells and for signal transmission between different immune cells.

Redox homeostasis for viral infection response should thus be offered. Oxidative stress and cell and tissue damage emerge when this equilibrium shifts in favor of excessive ROS generation or a deficit in the antioxidant defense system (Chernyak et al., 2020).

In general, oxidative stress impacts the development of illness in nearly all patients with viral infections, and these individuals can respond to the viral infection by maintaining their redox balance (Baloch et al., 2020).

5. Conclusion

In conclusion, this study provides insights into the potential role of oxidative stress in the pathogenesis of COVID-19. The assessment of oxidative stress biomarkers in COVID-19 patients may have clinical implications in identifying high-risk individuals and facilitating early intervention strategies. These findings have the potential to make valuable contributions towards the advancement of novel therapeutic approaches and create new opportunities for effectively managing patients with COVID-19.

Conflict of interest: The authors declare that they have no conflict of interests.

Informed consent: All participants received information about the study, and they all voluntarily signed and date the informed consent form. All participants in the trial, including patients and healthy volunteers, verbally consented after being fully informed (E-10840098-772.02-2667, 27-01-2021).

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