CHANGES IN SERUM NITRIC OXIDE LEVELS IN COVID-19 PATIENTS

COVID-19 Hastalarında Serum Nitrik Oksit Düzeylerindeki Değişiklikler

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ABSTRACT

Objective: Coronavirus 2 (SARS-CoV-2), the etiological agent of the COVID-19 pandemic that is rapidly affecting the entire world both in terms of health and economy, belongs to the beta coronavirus family. Although oxidative stress imbalance occurs in COVID-19 patients, how changing nitric oxide (NO) levels affect COVID-19 pathogenesis is not fully understood. For this purpose, NO levels were evaluated in the serum of COVID-19 patients.

Material and Methods: A total of 50 adult COVID-19 patients and 32 healthy control individuals were included in the study. COVID-19 patients were classified as Mild-COVID-19, Moderate-COVID-19, and Intensive Care-COVID-19 according to national guidelines. NO concentrations were measured spectrophotometrically from serum samples of all patients. Biochemical data were also collected.

Results: NO levels were lower in the patient group compared to the control group, but this difference was not statistically significant ($p>0.05$).

Conclusion: The variability in NO levels suggests that it may be a result of immune inflammation and vascular dysfunction in COVID-19 patients.

Keywords: *COVID-19; Free Radical; Nitric Oxide*

ÖZET

Amaç: Tüm dünyayı hem sağlık hem de ekonomik açıdan hızla etkileyen COVID-19 pandemisinin etiyolojik ajanı olan Koronavirüs 2 (SARS-CoV-2), beta koronavirüs ailesine aittir. COVID-19 hastalarında oksidatif stres dengesizliği meydana gelmesine rağmen, değişen nitrik oksit (NO) seviyelerinin COVID-19 patogenezini nasıl etkilediği tam olarak anlaşılmamıştır. Bu amaçla COVID-19 hasta serumlarında NO düzeyleri değerlendirildi.

Gereç ve Yöntemler: Çalışmaya toplam 50 yetişkin COVID-19 hastası ve 32 sağlıklı kontrol birey dahil edildi. COVID-19 hastaları ulusal kılavuzlara göre Hafif-COVID-19, Orta-COVID-19 ve Yoğun Bakım-COVID-19 olmak üzere sınıflandırıldı. NO konsantrasyonları tüm hastaların serum örneklerinden spektrofotometrik olarak ölçüldü. Ek olarak biyokimyasal verileri toplandı.

Bulgular: NO düzeyleri hasta grupta kontrol grubuna göre düşüktü fakat bu fark istatistiksel olarak anlamlı değildi ($p>0,05$).

Sonuç: NO seviyelerindeki değişkenlik COVID-19 hastalarında immün inflamasyon ve vasküler disfonksiyonun bir sonucu olabileceğini düşündürmektedir.

Anahtar Kelimeler: *COVID-19; Serbest Radikal; Nitrik Oksit*

INTRODUCTION

Coronavirus (SARS-CoV-2) first emerged in December 2019 in Wuhan Province, China. SARS-CoV-2 is a severe pathogenic human coronavirus (1). SARS-CoV-2 has been reported as the seventh human coronavirus to infect humans after HCoV-NL63, HCoV-229E, HCoV-OC43, HCoV-HKU1, SARS-CoV and MERSCoV. The disease caused by SARS-CoV-2 has been defined as COVID-19 by the World Health Organization (WHO) (2). As the disease spread rapidly and affected the whole world, WHO declared this disease a pandemic in March 2020 (3). While some cases are reported as symptomatic, some cases have symptoms such as fever, dry cough, shortness of breath and myalgia. In severe cases, cerebrovascular diseases, impaired consciousness, encephalopathy, encephalitis, peripheral nervous system damage, lung damage or multiple organ failure are observed (4). In severe COVID-19 cases, uncontrolled cytokine response triggers excessive endothelial inflammatory reactions and vascular thrombosis (5). The disruption of the balance between antioxidants and free radicals in biological systems is defined as oxidative stress (6). Recent studies show that oxidative stress plays an important role in viral infections such as SARS-CoV and SARS-CoV-2 infections (7-9). Nitric oxide (NO) was first identified as endothelium-derived relaxation factor (EDRF) (10). NO carries an unpaired electron in its last orbit and is therefore called a free radical. The role of NO depends on the place of production and its concentration. While all concentrations of other free radicals are quite dangerous for cells, low concentrations of NO have very important physiological functions. However, situations where NO synthesis is excessive and uncontrolled are harmful to the cell (11). Studies conducted to date have determined that NO is a very important regulatory molecule, second messenger and transmitter found in the cardiovascular, nervous, urogenital, digestive and immune systems. In addition to its physiological functions, it also plays a role in the pathophysiology of diseases such as neurodegenerative diseases, stroke, septic shock, and hypertension (12). Although oxidative stress imbalance is emphasized in COVID-19 patients, the contributions of NO formation to the pathogenesis of COVID-19 have not been sufficiently defined. It is known that NO, known as a free radical, has an important pathophysiological role in many systems, especially the nervous system, immune system, and cardiovascular system. In recent studies, the variability in NO levels in COVID-19 patient groups is particularly striking. For this reason, we aimed to understand the levels of NO in COVID-19 (+) patients and the effects of NO on COVID-19 disease pathophysiology and to investigate the development mechanisms of this disease.

MATERIALS AND METHODS

Ethical approval for this study was obtained from the Clinical Research Ethics Committee of Atatürk University School of Medicine (Approval number: 24.06.2021). The study was approved with the reference number B.30.2.ATA.0.01.00/36.

This study included 50 patients and 32 healthy volunteers diagnosed with nasopharyngeal and oropharyngeal swab samples and real-time polymerase chain reaction (RT-PCR) tests at Atatürk University Research Hospital between July and August 2021. The study population was divided into a healthy control group (HG) and a patient group (PG). All COVID-19 cases were managed in accordance with national guidelines.

RT-PCR positive patients (n=50) were further categorized based on disease severity into:

Mild COVID-19 (n=12): Symptomatic (fever, joint and muscle pain, cough, sore throat) without respiratory distress, respiratory rate <24/min, SpO_2 >93% on room air, and normal chest X-ray or CT.

Moderate COVID-19 (n=25): Symptoms similar to mild cases with respiratory rate <30/min, SpO_2 >90%, and mild to moderate pneumonia on chest imaging.

ICU-COVID-19 (n=13): Symptoms as above, with respiratory rate ≥30/min, SpO_2 ≤90%, and bilateral diffuse pneumonia on imaging.

Some of the blood samples were sent to the Atatürk University hospital laboratory for routine analysis and recorded with Neutrophil (NE), Lymphocyte (LY), pH, Carbon Dioxide (CO_2), Bicarbonate (HCO_3^-), Lactate (Lac), Methemoglobin (MetHb) and patient age information. The other part was sent to the Research Laboratory of the Department of Medical Biochemistry, Atatürk University Faculty of Medicine for NO analysis. Samples were stored at -80°C until the analysis day.

On the analysis day, samples were allowed to thaw gradually at +4°C. All samples were analyzed under the same conditions on the same day. NO levels in serum samples were measured by spectrophotometric method using a commercial colorimetric analysis kit (Cayman, Nitrate/Nitrite Colorimetric Assay kit (780001)). The intraassay coefficient of variation (CV) of the kit used was 2.7% and the interassay coefficient of variation (CV) was 3.4%.

Statistical Analysis

SPSS 21.0 (Statistical Package fort he Social Sciences v21.0 Armonk, NY: IBM Corp. 2012) package program was used for statistical analysis. Data were presented as mean±standard deviation, 95% Confidence Interval for Mean (Lower Bound-Upper Bound) and Interquartile Range. Kolmogorov-Smirnov test was used to determine the homogeneity of the data. Since data do not show normal distribution, Mann Whitney U test was used for paired group comparisons; and Kruskall Wallis test was used for three-group comparisons. Statistical significance level was taken as $p<0.05$ for all data.

RESULTS

The mean age was 50.80 (±18.8) in the patient group and 52.68 (± 14.86) in the healthy group. There was no statistically significant difference between the mean ages of the patient and control groups (p=0.637). Serum NO levels were lower in the patient group compared to the control group, but this decrease was not statistically significant (p= 0.052). However, both NE and LY counts were significantly decreased in COVID-19 patients compared to controls (p <0.001). These data are presented in Table 1.

A graphical comparison of serum NO levels between the control and patient groups is provided in Figure 1. Although NO levels tended to decrease in COVID-19 patients, the variation was high, particularly in the patient group, which may have contributed to the lack of statistical significance. This trend could reflect potential disruptions in NO metabolism due to viral pathogenesis and inflammatory responses, even in the absence of severe hypoxia.

In the analysis where COVID-19 patients were subdivided according to severity, NO levels tended to increase in parallel with the worsening of the clinical picture. The mean NO levels in the mild, moderate, and intensive care unit (ICU) groups were 3.83 ± 2.56 µM/L, 4.79 ± 2.64 µM/L, and 5.43 ± 2.92 µM/L, respectively (p = 0.339). The median values were 3.02, 4.60, and 5.14 µM/L, respectively.

The box plot presented in Figure 2 visually supports this trend. The plot shows a increase in median NO levels as disease severity increases. In the ICU group, both the median and upper quartile values were found to be higher than in the other groups. This suggests that nitric oxide levels, a marker of oxidative stress, increase with advanced disease severity. However, statistical analysis revealed no significant difference between the groups (p> 0.05). Therefore, although the observed trend toward an increase in NO levels was clinically significant, it could not be statistically confirmed.

Among the biochemical parameters evaluated, pH levels were found to be significantly higher in the ICU-COVID-19 group compared to the other subgroups (p = 0.027), possibly indicating a compensatory respiratory alkalosis in critically ill patients. Other parameters, including NE, LY, CO_2, HCO_3, lactate, and MetHb, did not differ significantly across COVID-19 subgroups (p> 0.05).

Table 1. Age and Biochemical Values of The Healthy Control Group and Patients with COVID-19 (+)

Groups	PG (n:50)			HG (n:32)			P value
	Mean±SD	Med (IQR)	%95(CI)	Mean±SD	Med (IQR)	%95(CI)	
LY (×10^3)	1477.8±834.88	1250(855)	1240.5-1715	2539.6±1150.7	2295 (2202.5)	2124.7-2954.5	0.001*
NE(×10^3)	3829.4±1746.2	3555(2152.5)	3333.1-4325.6	5396.9±2193.2	4588.5 (3832)	4606.1-6187.6	0.001*
NO(µM/L)	4.73±2.7	4.44 (4.19)	3.96 - 5.5	6.02±2.9	5.1(3.45)	4.97-7.07	0.052
Age (year)	50.82±18.8	48.5(27.25)	45.45- 56.18	52.68±14.86	51 (22.25)	47.3 -58.04	0.637

*: Statistically signifiant. PG: COVID-19 (+) patien tgroup; HG: Healthy control group. NO: Nitric Oxide, NE: Neutrophil, LY: Lymphocyte SD: Standard deviation; Med:Median (IQR: InterquartileRange), CI: Confidence Interval for Mean

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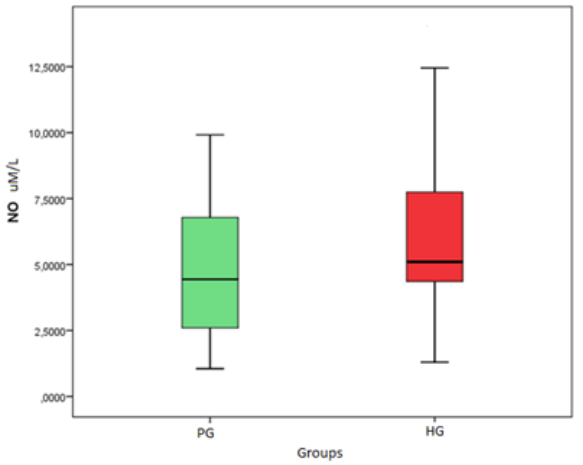

Figure 1. Serum NO Levels in Control and COVID-19(+) Patient

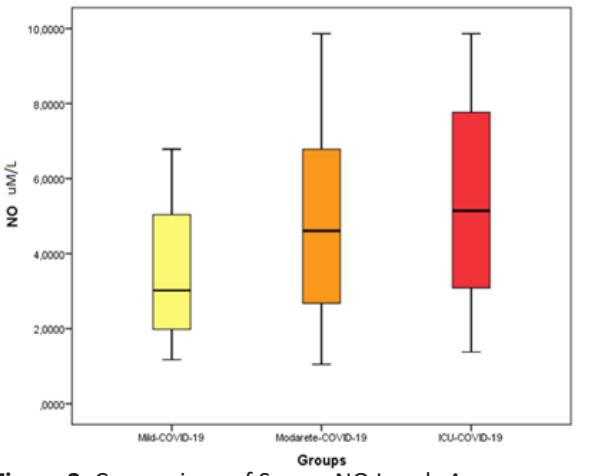

Figure 2. Comparison of Serum NO Levels Among COVID-19 Subgroups Based on Disease Severity

DISCUSSION

Following the declaration of COVID-19 as a pandemic by the WHO, numerous studies have been conducted on the pathogenesis, course, and treatment approaches of the disease. A significant portion of these studies have focused on NO, which plays a critical role in processes such as the immune response, endothelial dysfunction, and hypoxia. NO stands out as a potential marker and therapeutic target in the clinical picture of COVID-19 due to its both immune response-modulating and vasodilatory effects.

The effects of NO vary depending on the stage of infection, the degree of tissue hypoxia, intracellular antioxidant capacity, and the isoforms in which it is synthesized (13).

Studies have shown notable differences in NO levels in COVID-19 patients. Some studies have reported decreased NO levels in COVID-19 patients due to increased oxidative stress and endothelial dysfunction. This decrease in NO levels has been attributed to the formation of peroxynitrite ($ONOO^-$) as a result of interactions with reactive oxygen species (ROS) and subsequent NO depletion. Therefore, monitoring nitrite/nitrate (NOx) levels and even supplementing them with exogenous nitrate or nitrite have been recommended in COVID-19 patients (14,15). Some studies have shown that NO levels in the patient group are significantly higher than in healthy individuals. This increase has been attributed to macrophage activation, which is common during inflammatory immune responses. Following inflammation, the amount of inducible nitric oxide synthase (iNOS) in macrophages can increase 2-3-fold, causing the release of large amounts of NO, leading to local and systemic increases in nitrate or nitrite (16-18).

In our study, serum NO levels were found to be lower in COVID-19 patients compared to healthy controls. However, this difference was not statistically significant. Our findings are consistent with those of Özdemir & Yazıcı and Fang et al., while consistent with the studies conducted by both studies, our results are supported by demonstrating that decreased endothelium-derived nitric oxide (NO) production and NO bioavailability may play a critical role in COVID-19-related deaths (19,20).

Interestingly, some studies, particularly in severe cases and intensive care patients, have found increased NO production due to increased iNOS expression due to macrophage activation. Mandal made a noteworthy point in this regard: in some cases, NO levels were found to be higher in COVID-19 patients than in non-COVID hypoxemic cases, and this was associated with a silent hypoxemia condition called "happy hypoxia." He emphasized that increased NO levels, particularly in erythrocytes, can facilitate oxygen release to the tissue, while excessive NO accumulation can cause mitochondrial dysfunction, triggering apoptosis and cellular damage (13).

In our study, when examining COVID-19 subgroups, the highest NO levels were observed in intensive care patients and the lowest in mild cases, but these

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Table 2. Biochemical values of patient subgroups with COVID-19 (+)

GROUPS		Subgroups of PG			
		MildCOVID-19 (n=12)	ModareteCOVID-19(n=25)	ICUCOVID-19 (n=13)	P value
Age (year)	Mean±SD	37.42 ± 17.69	53 ± 18.93	59 ± 13.80	0.151
	Med (IQR)	35 (27)	50 (28)	59 (23)	
	%95(CI)	26.17 - 48.66	45.18 - 60.82	50.66 - 67.34	
NO(µM/L)	Mean±SD	3.83 ± 2.56	4.79 ± 2.64	5.43 ± 2.92	0.339
	Med (IQR)	3.02 (3.84)	4.6 (4.2)	5.14 (5.52)	
	%95(CI)	3.69 - 5.88	3.69 - 5.88	3.67 - 7.2	
NE($\times10^3$)	Mean±SD	3908.3 ±2306.1	3499.6 ±1609.9	4390.77 ± 1347.3	0.48
	Med (IQR)	3285 (1783)	3460 (2154)	4390 (1905)	
	%95(CI)	2443.09-5373.57	2835.04 -4164.16	3576.6 - 5204.94	
LY ($\times10^3$)	Mean±SD	1815 ± 971.42	1478.8 ± 887.54	1164.6 ± 431.01	0.330
	Med (IQR)	1660 (972.5)	1170 (980)	1000 (570)	
	%95(CI)	1197.7 - 2432	1112.44 -1845.15	904.15 -1425.07	
pH	Mean±SD	7.38 ± 0.17	7.41 ± 0.02	7.43 ± 0.04	0.027*
	Med (IQR)	7.38 (0.02)	7.41 (0.04)	7.42 (0.08)	
	%95(CI)	7.39 - 7.4	7.39 - 7.43	7.4 - 7.46	
CO_2 (mmHg)	Mean±SD	42.06 ± 1.82	43.16 ± 8.72	41.87 ± 10.65	0.933
	Med (IQR)	41.75 (2.6)	42.8 (12.22)	36.9 (21.6)	
	%95(CI)	40.15 - 43.97	37.62 - 48.7	34.71 - 49.02	
HCO_3(mEq/Lt)	Mean±SD	24.01 ± 1.39	24.8 ± 2.24	23.72 ± 1.55	0.373
	Med (IQR)	23.6 (2.1)	24.35 (3)	23.8 (2.7)	
	%95(CI)	22.55 -25.48	23.38 - 26.23	22.68 - 24.77	
Lactate	Mean±SD	1.23 ± 0.24	1.34 ± 0.43	1.5 ± 0.59	0.523
	Med (IQR)	1.2 (0.25)	1.35 (0.47)	1.4 (0.9)	
	%95(CI)	0.97 - 1.48	1.06 - 1.62	1.1 - 1.89	
MetHb	Mean±SD	1.56 ± 0.17	1.55 ± 0.21	1.5 ± 0.26	0.781
	Med (IQR)	1.55 (0.3)	1.55 (0.5)	1.55 (0.3)	
	%95(CI)	1.38 - 1.75	1.42 - 1.69	1.32 - 1.67	

PG: COVID-19(+) patient group NO :Nitric Oxide, NE :Neutrophil, LY: Lymphocyte, pH:Potential hydrogen, CO_2: Carbondioxide, HCO_3: Bicarbonate, MetHb: methemoglobin, SD: Standard deviation; med: Median (IQR: Interquartile Range), CI: Confidence Interval for Mean.

differences were not statistically significant. This finding suggests that increased NO production may occur as a compensatory mechanism against hypoxia in later disease stages. Furthermore, as highlighted in Mandal's study, increased mitochondrial NO levels during periods of low partial oxygen pressure and their resulting inhibition of the respiratory chain can lead to impaired cellular energy production.

Another notable observation in our study was the significantly decreased neutrophil and lymphocyte counts in COVID-19 patients, supporting the hypothesis of immune suppression or redistribution during active infection. The markedly elevated pH levels in intensive care patients may reflect respiratory alkalosis due to increased ventilatory drive, a known compensatory response in intensive care patients.

Taken together, our findings suggest that although serum NO levels tend to decrease in COVID-19, especially in the early stages, dynamic changes occur throughout the disease. Further longitudinal studies are needed to clarify the clinical significance of NO fluctuations and their potential role in guiding treatment or prognosis.

CONCLUSION

When examining clinical subgroups based on COVID-19 disease severity, NO levels differ. This reflects various factors related to disease mechanisms, individual responses, and differences in analytical methods. Therefore, prospective and standardized studies are still necessary to better understand NO's role not only in COVID-19 progression but also in its long-term effects and potential as a biomarker for similar respiratory infections.

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