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Investigation of paraoxonase1 enzyme activity and Q/R 192 polymorphism in severe COVID-19 cases

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Abstract

COVID-19, an infection associated with numerous cases and deaths globally since 2019, has been a subject of extensive research. Paraoxonase1 (PON1), recognized for its antioxidant activity and contribution to the reduction of oxidative damage, is the focus of this study. The research aims to measure the activity of the human serum PON1 enzyme with detoxification and antioxidant properties in COVID-19 cases leading to pneumonia. Additionally, the phenotype of the PON1 Q/R 192 polymorphism is investigated and compared with a control group. The study includes 26 severe COVID-19 cases and 24 healthy individuals. The phenotype distribution of patients is determined as 38.48% QQ, 53.83% QR, and 7.69% RR, while in the control group, these percentages are 50.00% QQ, 29.17% QR, and 20.83% RR. Furthermore, PON1 activity is measured in 26 COVID-19 patients and 24 healthy individuals. The results indicate distinct differences in the phenotype distribution of the PON1 Q/R 192 polymorphism between COVID-19 patients and the control group. The percentages of QQ, QR, and RR are unique in both groups. Additionally, PON1 activity is measured, revealing that the control group exhibits higher PON1 activity compared to the affected individuals.

Keywords: *Paraoxonase1, SARS-CoV-2, COVID-19, Q/R 192R polymorphism.*

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Ağır COVID-19 geçiren hastalarda paraoksonaz1 enzim aktivitesinin ve Q/R 192 polimorfizminin araştırılması

Öz

COVID-19, 2019 yılından bu yana dünya genelinde çok sayıda vaka ve ölümle ilişkilendirilen bir enfeksiyon olup, kapsamlı araştırmalara konu olmuştur. Antioksidan aktivitesi ve oksidatif hasarın azaltılmasına katkısı ile bilinen Paraoksonaz1 (PON1), bu çalışmanın odak noktasını oluşturmaktadır. Araştırma, zatürreye yol açan COVID-19 vakalarında detoksifikasyon ve antioksidan özelliklere sahip insan serum PON1 enziminin aktivitesini ölçmeyi amaçlamaktadır. Ayrıca, PON1 Q/R 192 polimorfizminin fenotipi incelenmiş ve bir kontrol grubu ile karşılaştırılmıştır. Çalışma, 26 ağır COVID-19 vakası ve 24 sağlıklı bireyi içermektedir. Hastaların fenotip dağılımı %38,48 QQ, %53,83 QR ve %7,69 RR olarak belirlenirken, kontrol grubunda bu oranlar sırasıyla %50,00 QQ, %29,17 QR ve %20,83 RR olarak bulunmuştur. Bunun yanı sıra, 26 COVID-19 hastası ve 24 sağlıklı bireyde PON1 aktivitesi ölçülmüştür. Sonuçlar, COVID-19 hastaları ile kontrol grubu arasında PON1 Q/R 192 polimorfizminin fenotip dağılımında belirgin farklılıklar olduğunu göstermektedir. QQ, QR ve RR yüzdeleri her iki grupta da benzersizdir. Ayrıca, PON1 aktivitesi ölçümleri, kontrol grubunun etkilenen bireylere kıyasla daha yüksek PON1 aktivitesi sergilediğini ortaya koymaktadır.

Anahtar kelimeler: *Paraoksonaz1, SARS-CoV-2, COVID-19, Q/R 192R polimorfizim.*

1. Introduction

In December 2019, a pneumonia outbreak characterized by an unidentified cause emerged within the city of Wuhan, situated in China's Hubei province. In response to the escalating count of cases spreading beyond national borders, the World Health Organization (WHO) declared a global health emergency on January 30, 2020 [1]. The pathogen responsible for this illness, known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in widespread infections and fatalities across the globe [2]. Individuals infected with SARS-Cov-2 often experience upper respiratory tract symptoms such as fever, cough, nasal congestion and fatigue. Approximately 75% of these individuals have prominent chest findings corresponding to shortness of breath and pneumonia symptoms. Pneumonia usually appears in the clinic in the later weeks of infection, especially in the second or third week. Decreased oxygen saturation, abnormalities in blood gases, specific findings on radiological imaging and ground glass opacities play a critical role in the diagnosis of viral pneumonia [3]. Today, as a result of the measures taken, the vaccines developed and the mutations occurring in the virus, there are no major problems on a global scale. However, the rapid transmission ability of the virus in question and the infection it causes affect people's quality of life and cause a great loss of workforce. For a successful infection, viral pathogens manipulate the host metabolism to create a suitable habitat for themselves. The metabolic resources within the host cell play a crucial role in synthesizing various viral components, including viral nucleic acids, proteins, and membranes. Many viruses adeptly manipulate the host cell's metabolism to optimize their

own biosynthetic requirements, inducing specific metabolic alterations that favor viral replication and proliferation [1]. On the other hand, different metabolic strategies have been designed to inhibit viral replication through antiviral metabolic changes in host cells [2]. Oxidative stress produced in host cells during this process is thought to cause mitochondrial dysfunction. As a natural consequence, more free radicals will be produced in the affected tissue [4].

Indeed, the innate immune system encompasses mechanisms designed to shield against oxidative stress, with the PON protein family standing out as one of its pivotal components. These enzymes are a group of proteins in three forms encoded by the PON1, PON2 and PON3 genes. PON1, the most studied isoenzyme in this protein group, is a metalloenzyme synthesized in the liver and circulating in the circulation bound to high-density lipoproteins. PON1, whose primary structure consists of 355 amino acid residues, contains two calcium ions. One of these ions is involved in the stabilization of the three-dimensional structure of the enzyme, while the other is known to be critical in the catalytic mechanism of PON1 [5].

PON1 has important roles in the organism with antioxidant, anti-atherosclerotic and anti-inflammatory effects with a wide range of substrate specificity. The PON family plays a crucial role in impeding the oxidative modification of low-density lipoprotein (LDL), thereby effectively suppressing the transition of monocytes into macrophages. This inhibition marks the initial stage of preventing the progression of atherosclerosis, a condition characterized by the accumulation of plaque in arteries. Additionally, PON1 stimulates cholesterol efflux from macrophages, preventing the accumulation of oxidized LDL. Indeed, extensive research has focused on investigating the enzymatic activity of the PON family, particularly the role of PON1, in relation to the development of various diseases. These studies have delved into its potential implications in conditions ranging from cancer and cardiovascular ailments to neurological disorders and inflammatory diseases. Understanding the involvement of PON1 has been a critical pursuit in unraveling the mechanisms underlying these diverse health conditions [5–8]. It has also been shown that serum PON1 activity in patients with HIV infection is reduced compared to the normal population, and these changes are associated with the patients' immunological status and degree of inflammation [9]. Apart from this, researchers have reported that oxidative stress increases and serum PON1 activities decrease in other viral infections such as influenza, hepatitis B and hepatitis C [9–12].

The polymorphism in the coding region, which affects the activity and level of PON1, occurs as a result of the substitution of glutamine (Q) and arginine (R) amino acids at codon 192 [13]. The Q192 isoform has a higher paraoxon hydrolyzing capacity than the R192 isoform and also metabolizes oxidized LDL more effectively. Polymorphic variations of PON1 may vary depending on ethnicity, gender, age, and environmental factors [9]. Activity and polymorphism variations of the PON1 enzyme have been associated with many pathological conditions [10,14]. The effect of Q192R polymorphism on oxidative status has been identified as a biomarker. Inhibition of LDL oxidation, especially QQ, is highest in homozygous individuals, while RR is lowest in homozygous individuals [15]. PON1 has been identified and researched as a potential therapeutic tool against atherosclerosis development [16]. However, investigations into the association between the PON1Q192R polymorphism and cardiovascular diseases have yielded conflicting results. While certain studies have indicated a positive link between the PON1192RR genotype and coronary disease, this relationship remains a

topic of contention in scientific research [9,13]. While others found no association [10,15,17]. It states that infectious diseases such as COVID-19 are associated with oxidative stress and inflammatory responses [4,9]. Additionally, a potential association between the prevalence and mortality rates of COVID-19 and the L55M functional polymorphism of PON1 has been identified [18]. In this study, PON1 activities in patients with severe COVID-19 will be determined and the distribution of PON1 Q192R polymorphism will be investigated. An idea will be obtained about the effect of this genetic variation against COVID-19 by comparing it with healthy individuals.

2. Material and method

2.1. Materials

Paraoxon-ethyl, Tris-Base and NaCl (sodium chloride) compounds were supplied from Sigma-Aldrich. Bio-Tech UV spectrophotometer was used in the experiments. Approval from the relevant ethics committee was obtained to conduct the study. (Çankırı Karatekin University Health Sciences Ethics Committee, Çankırı, Turkey, Meeting No: 27 Date: 10.10.2022)

2.2. Collection of blood samples

Blood samples were collected from; 26 patients with symptoms of fever, muscle and joint pain, cough, sore throat, tachypnea (≥30/minute), SpO2 level ≤ 90% in room air, and bilateral pneumonia findings detected in radiological examinations were included. As the control group, 24 healthy individuals who had not previously had COVID-19 infection were selected. Immediately after blood samples were taken, they were centrifuged at 3000 rpm for 10 minutes and the resulting sera were stored at -80°C. Informed consent forms were obtained from all individuals.

2.3. Measurement of PON1 enzyme activity

Measurement of PON1 enzyme activity was performed according to the protocol described by Eckerson et al. [19]. According to this methodology, the hydrolysis rate of paraoxon was determined spectrophotometrically as the absorbance change over a period of 1 min at a wavelength of 412 nm at a temperature of 37 °C. Activity values were calculated using an extinction coefficient of 17100 M^{-1} cm^{-1}. One unit (U) of paraoxonase activity was expressed as 1 µmol *p*-nitrophenol formed per minute. Paraoxon substrate was prepared fresh before each experiment.

2.4. PON1 phenotype analysis

For the phenotypic analysis of the paraoxonase enzyme, basal and post-salt stimulation activities were measured, and the phenotype was determined through the following formula:

$$\frac{Paraoxonase\ Activity - Basal\ Paraoxonase\ Activity\ in\ the\ presence\ of\ 1\ M\ NaCl}{Basal\ Paraoxonase\ Activity} \text{x100}$$

With this analysis method, three different activity distribution was observed. As a result of the formula, values up to 60% represent low-activity homozygous QQ, values between 60-200% represent medium-activity heterozygous QR, and values of 200% and above represent high-activity homozygous RR [20].

2.5. Statistical analyses

Statistical analysis was performed using Microsoft Excel for Windows. When more than two groups were compared, analysis of variance, ANOVA, was used. Data are presented as mean ± standard deviation.

3. Results and discussion

The COVID-19 pandemic has deeply affected human health globally. This health crisis caused by the SARS-CoV-2 virus has led scientists to in-depth research on this subject [21]. In this scientific study, the potential relationship of PON1 polymorphism with COVID-19 was investigated. The study included patients who were diagnosed with COVID-19, had symptoms such as fever, muscle-joint pain, cough and sore throat, had tachypnea (≥30/minute), had SpO2 levels measured below 90% in room air, and had chest radiography or tomography. 26 patients (10 women, 16 men) with bilateral widespread pneumonia findings participated. As a control group, 24 healthy individuals (15 women, 9 men) who did not show any symptoms of pneumonia and did not have COVID-19 infection were included in the study. Blood serum samples from both groups were collected for analysis.

In this study, serum PON1 activities of all individuals were determined individually. Then, the arginine/glutamine (R/Q) polymorphism at position 192 was detected in individuals by the method mentioned above. The values found in the research are summarized in Table 1 and Table 2. Activity and polymorphism results of all individuals are not given considering the scope of the article. It was determined that 11 (42.30%) of 26 patients had QQ, 13 (50%) QR and 2 (7.69%) RR genotypes. It was determined that 13 (54.16%) of the individuals in the control group had QQ, 6 (25%) QR and 5 (20.83%) RR genotypes (Table 1). Additionally, the PON1 activity of the control group (31.9 ±10.4) was found to be higher than the patient group (23.8 ±10.1) (Table 2).

Although the paraoxonase enzyme has many polymorphisms, the arginine/glutamine (R/Q) polymorphism at position 192 attracts particular attention. PON1 is produced in the liver and circulates bound to high-density lipoprotein HDL, and plays an antioxidant role by inhibiting LDL oxidation. Additionally, it has been determined that PON1 is of critical importance in protecting individuals from various diseases thanks to its anti-inflammatory and detoxification properties [22–24]. Therefore, there are findings in the literature that PON1 activity and polymorphism are associated with cardiovascular diseases, pulmonary disease, diabetes, Alzheimer's and cancer risk [23–27]. Studies on PON1 polymorphism in the literature have stated that the RR phenotype is frequently observed among individuals with coronary heart disease, and among Alzheimer's patients, those carrying the R allele have higher serum PON1 activity than those carrying the Q allele [14]. In another study conducted on PON1 polymorphism (rs662), the effect of PON1 polymorphism on disease severity and mortality in COVID-19 patients was evaluated by examining the lipid profile and arylesterase (ARE) activity of PON1 in 470 COVID-19 patients.

This study showed that PON1 polymorphism may affect COVID-19 disease severity and mortality [28]. The genetic distribution of paraoxonase may vary among different ethnicities. In a study conducted on the Turkish population, it was determined that the genotype distribution was 46.7% QQ, 44.6% QR and 8.7% RR [29]. During previous

epidemics and the COVID-19 pandemic, it has been suggested that viral infections vary depending on ethnicity and environmental factors [30].

Our results show that the PON1 activity of patients with severe COVID-19 infection is lower than that of the healthy control group. Oxidative stress markers, such as paraoxonase (PON) activity, have been shown to play a significant role in the prognosis and follow-up of patients in intensive care, particularly in conditions involving trauma [31] and severe infections like COVID-19. Similar to findings in osteoporosis, where reduced PON1 activity is associated with increased oxidative stress and bone loss, our study also highlights the potential role of decreased PON1 activity in exacerbating oxidative damage in severe COVID-19 cases [32]. Furthermore, in conditions such as polycystic ovary syndrome (PCOS), reduced PON1 activity has been linked to increased cardiovascular risk and hormonal imbalances, further supporting the notion that PON1 plays a critical role in modulating oxidative stress and inflammatory responses across various diseases [33]. Moreover, recent studies have demonstrated that PON1 activity can be significantly inhibited by various drugs, such as furosemide and enrofloxacin, with furosemide showing a stronger inhibitory effect (IC_{50} = 9.87 mM) compared to enrofloxacin (IC_{50} = 42.21 mM), further emphasizing the importance of understanding drug-enzyme interactions in the context of oxidative stress and disease progression [34]. Recent studies have shown that PON1 activity varies significantly across different species, with purification methods such as ammonium sulfate precipitation and hydrophobic interaction chromatography yielding high-specific activity enzymes, as demonstrated in bovine breeds like Swiss Black, Holstein, and Montofon [35].

These findings suggest that individuals with low PON1 activity may be more susceptible to a severe course of COVID-19 infection. This is consistent with the literature, which supports a relationship between PON1 activity and the severity of viral infections. Additionally, we observed distinct differences in the phenotype distribution between COVID-19 patients and the control group. Specifically, the QQ phenotype was more prevalent in the control group, while the QR phenotype was more common in the patient group. This indicates that the PON1 Q192R polymorphism may be associated with either susceptibility to COVID-19 or the severity of the disease.

The findings of this study are consistent with previous reports on the genotype distribution in the Turkish population [29]. However, these results may not fully represent of the general Turkish population, as viral infections can vary depending on ethnic and environmental factors, and the sample size is limited. Despite these limitations, our study suggests a possible association between COVID-19, paraoxonase 1 (PON1) activity, and the Q192R polymorphism. Given the crucial role of PON1 in reducing oxidative stress, our findings indicate that COVID-19 may alter oxidative stress levels in the body, potentially leading to a decrease in PON1 activity. We believe that these results will contribute to a deeper understanding of COVID-19 pathogenesis and may have implications for future therapeutic strategies.

Table 1. Phenotyping of the control and patient groups.

	PON1 Activity (in 1M NaCl) U		Basal PON1 Activity U		Phenotype	
No	**Control**	**Patient**	**Control**	**Patient**	**Control**	**Patient**
1	353.7	358.6	108.1	153.5	RR	QR
2	239.5	154.7	153.5	94.5	QQ	QR
3	176.8	184.2	119.1	84.7	QQ	QR
4	265.3	43.0	27.0	23.3	RR	QR
5	192.8	142.5	128.9	89.6	QQ	QQ
6	200.9	110.5	149.8	58.9	QQ	QR
7	254.2	144.9	46.7	40.5	RR	RR
8	332.8	82.3	136.3	13.5	QR	RR
9	165.8	104.4	105.6	88.4	QQ	QQ
10	143.7	77.4	105.6	36.8	QQ	QR
11	200.2	126.5	94.6	50.3	QR	QR
12	190.3	224.7	120.3	82.2	QQ	QR
13	272.6	165.7	70.00	77.3	RR	QR
14	194.0	200.1	100.7	115.4	QR	QR
15	243.2	160.8	157.2	85.9	QQ	QR
16	178.1	141.2	81.1	116.6	QR	QQ
17	133.9	244.3	100.7	111.7	QQ	QR
18	244.4	52.8	111.7	30.7	QR	QR
19	264.0	111.7	52.8	98.2	RR	QQ
20	202.6	23.3	94.6	22.1	QR	QQ
21	230.9	34.3	162.1	22.1	QQ	QQ
22	170.7	111.7	146.1	51.5	QQ	QR
23	174.4	101.9	160.9	70.0	QQ	QQ
24	194.0	44.2	117.9	30.7	QR	QQ
25		40.5		17.1		QR
26		60.1		44.2		QQ

Table 2. Phenotype percentages and demographic characteristics of the patient and control groups.

PHENOTYPE	**PATIENT (n=26) (10 women and 16 men)**	**CONTROL (n=24) (15 women and 9 men)**
QQ (Homozygous)	%42.30	%54.16
QR (Heterozygous)	%50	%25
RR (Homozygous)	% 7.69	%20.83
Age (± SDI)	66.7 (±17.9)	37.5 (±12.1)
PON1 activity (U/µl dak)	23.8 (±10.1)	31.9 (±10.4)

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