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Evaluation of elabela, visfatin, and chemerin levels as inflammation biomarkers in COVID-19

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Abstract. – OBJECTIVE: The aim of this study was to investigate if inflammation biomarkers elabela, visfatin, and chemerin will be useful in the diagnosis of patients with COVID-19.

PATIENTS AND METHODS: This prospective case-control study included 33 patients with COVID-19 and 30 healthy matched controls. 33 patients, aged 18 years and older, diagnosed with COVID-19 and followed up for one month were included in the study. Blood samples were taken from the patients on the first day they were diagnosed with COVID-19, and levels of elabela (ELA), visfatin, chemerin, white blood cells (WBC), C-reactive protein (CRP) and procalcitonin (PCT) were assessed. Blood samples were also taken from 30 healthy volunteers for the control group. The ELA, visfatin and chemerin levels measured in the patients on day one were compared with those measured in the control group and with the WBC, CRP and PCT levels measured in the patients.

RESULTS: Visfatin levels measured in COVID-19 patients were significantly higher than in the healthy control group. There was no significant difference in ELA and chemerin levels between the two groups. A significant positive correlation was found between chemerin and visfatin levels in the patients. A significant negative correlation was found between the levels of ELA-chemerin and ELA-visfatin in the patients. There was no significant correlation between elabela, visfatin and chemerin levels and WBC, CRP, PCT levels.

CONCLUSIONS: Measurement of visfatin levels may be helpful in patients with COVID-19. However, two other biomarkers in our study, ELA and chemerin, were found not to be useful in diagnosing COVID-19. New inflammatory biomarkers may help to diagnose a disease in which the inflammatory response is at the forefront, such as COVID-19. New studies are needed on this subject.

Key Words:
COVID-19, Elabela, Visfatin, Chemerin.

Introduction

COVID-19 is a new type of coronavirus disease that was first identified in late December 2019 due to research conducted on a group of patients who developed fever, cough and shortness of breath in Wuhan, China. From the start of the outbreak to the end of 2022, it caused more than 650 million diagnosed cases and more than 6.5 million deaths worldwide over a two-year period. Although its diagnosis is mainly based on real-time PCR and imaging techniques, the widespread inflammatory response and cytokine storm that occurs in the body in response to the virus results in changes in the levels of many biomarkers that can aid in diagnosis[1,2] ELA, visfatin and chemerin are three important biomarkers that have emerged in recent years. Their role in the diagnosis and prognosis of many diseases has been studied. In our study, we aimed to investigate their prognostic role in the diagnosis of COVID-19.

Patients and Methods

This study is a single-center, prospective cohort study. In the study, 33 COVID-19 patients aged 18 years and older who were hospitalized in our center for a period of 1 month were included. The diagnosis of COVID-19 was made with Real-time PCR in samples taken by the nasopharyngeal swap method. White blood cell (WBC), C-reactive protein (CRP), and procalcitonin (PCT) values were measured by taking blood samples on the first day from patients diagnosed with COVID-19 by real-time PCR. Simultaneously, blood samples were taken from the patients, centrifuged, and serum separated. It was then stored at -80 degrees to safely store the values of elabela (ELA), visfatin and chemerin in bulk until the study time. In addition, blood samples were taken from 30 people with a body mass index (BMI) <25 kg/m^2, who did not have any chronic disease, did not use regular medication, and were used as a control group to determine the values of the biomarkers of ELA, visfatin and chemerin in the healthy population. Before the study of the ELA, visfatin

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and chemerin values of the patients, the blood was removed from -80 degrees and dissolved under appropriate conditions. The results of all kits were read using theBio Tek ELx800 (BioTek Instruments, Inc. Vermont, USA). The measurements obtained in this way from the patient and healthy control group were recorded in the database we created for later statistics.

Measurement of Serum Elabela

Serum prolidase enzyme activity was determined using a commercially available quantitative enzyme-linked immune sorbent assay (ELISA) technique (Sunred Biotechnology Company, Shanghai, China) according to the manufacturer's instructions. Serum Elabela enzyme levels were shown as pg/mL.

Measurement of Serum Visfatin

Serum visfatin levels were measured using a commercial quantitative ELISA technique (Elabscience Company, TX, USA) according to the manufacturer's instructions. Serum visfatin levels were shown as ise ng/mL.

Measurement of Serum Chemerin

Serum chemerin levels were measured by using a commercial quantitative ELISA technique (Elabscience Company, TX, USA) according to the manufacturer's instructions. Serum chemerin levels were shown as ng/mL.

Statistical Analysis

The calculations were performed using the Statistical Package for Social Sciences software version 22.0 (IBM Corp., Armonk, NY, USA) for Windows. The Kolmogorov-Smirnov test confirmed that data were within the normal distribution ranges in both groups. A nonparametric test was employed for the variables outside the normal distribution. The comparison of the data between reciprocal groups was carried out through the Mann-Whitney U and Chi-square test. Pearson's correlation analysis was used for the relationship between normally distributed variables, and Spearman's correlation analysis was used for the relationship between non-normally distributed variables. Statistical significance was based on a value of $p<0.05$ with a 95% confidence interval.

Results

The mean age of the 33 patients included in the study was 46.1±19.75 (min: 18; max: 82), 19 (57.6%) of the patients were males, and 14 (42.4%) were females. Of the patients, 29 (87.9%) were followed up in the COVID-19 clinic and 4 (12.1%) in the COVID-19 intensive care unit. Considering the comorbidities, hypertension was present in 12 (36.4%) patients, and hypertension was not found in 21 (63.6%) patients. Thirty of the patients were discharged with recovery, and three patients died. All demographic data of the patients are given in Table I.

ELA, visfatin, and chemerin values found in the blood samples taken from the patient group were compared with those in the blood taken from the healthy control group. The visfatin values detected in the patients were significantly higher than in the control group ($p=0.002$). The two groups had no significant difference regarding elabela and chemerin values (p-values 0.087 and 0.162, respectively). The findings are given in Table II.

Correlations of WBC, CRP, PCT, ELA, visfatin and chemerin values detected in the blood taken on the first day of the patients were evaluated. A significant negative correlation was found in the patient group between ELA values detected

Table I. Demographic data.

Characteristic	Mean±SS or number (%), (n: 50)
Age	46.1±19.75
Gender	
Female	14 (42.4%)
Male	19 (57.6%)
Service	
COVID-19 Clinic	29 (87.9%)
COVID-19 Intensive care	3 (12.1%)
Additional Diseases	
Hypertension	
Yes	12 (36.4%)
No	21 (63.6%)
Fewer	
Yes	12 (36.4%)
No	21 (63.6%)
Antibiotic	
Yes	23 (69.7%)
No	10 (30.3%)
Steroid	
Yes	4 (12.1%)
No	29 (87.9%)
Favipravir	
Yes	8 (24.2%)
No	25 (75.8%)
Anti-TNF	
Yes	1 (3%)
No	32 (97%)
Status	
Lives	30 (90.9%)
Exitus	3 (9.1%)

Anti-tumor necrosis factor (anti-TNF).

on the first day and visfatin and chemerin values (p-values of 0.039 and 0.047, respectively). A significant positive correlation was found between chemerin and visfatin values (p=0.016). Correlations of three biomarkers with patients' biochemistry and hemogram parameters were also evaluated. While a significant positive correlation was found between elabela values and platelet values (p=0.05), a significant negative correlation was found between elabela and aspartate transaminase (AST) values (p=0.011). No significant correlation was found between other parameters. Correlations are given in Table III.

Discussion

COVID-19 is a viral infectious disease that can affect all age groups and cause morbidity and mortality. In the study by Gautret et al[3] of COVID-19 patients, the median age was 45.1±22.0 years and 58.3% of the participants were females and 41.7% males. In the study of Munblit et al[4], the median age was 56 (46-66 years) and 51.1% of the patients were females and 48.9% were males. Similarly, in our study, the mean age of the patients was 46.1±19.75 years, 57.6% were males and 42.4% were females.

ELA is a molecule defined as a hormone with a polypeptide structure discovered as an endogenous ligand of the apelinergic system[5]. It is a molecule that has been studied in many subjects since its discovery and continues to be studied intensively. In their study, Yang et al[6] showed that ELA has many effects on the cardiovascular system by binding to its receptors in the cardiovascular endothelium. In their study in rats, they showed that ELA increased cardiac contractility, increased ejection fraction and, therefore, cardiac output, and had a potent vasodilator effect. This study also reported that ELA expression in cardiac tissue was reduced in rats with pulmonary arterial hypertension and that pulmonary arterial hypertension was improved by a significant reduction in right ventricular hypertrophy and pulmonary vascular remodeling after ELA treatment in these rats.

When we reviewed the literature, we did not find any studies of elabela in patients with COVID-19, although it has been studied in diseases such as community-acquired pneumonia and pulmonary hypertension.

Since the data presented suggest that this newly discovered molecule can be an excellent inflammatory biomarker, in this study in which we evaluated COVID-19 patients, ELA levels in COVID-19 patients were compared with the

Table II. Study-control group values of biomarkers.

	Study Group		Control Group		
	Median±SS	Median (min-Max)	Median±SS	Median (min-Max)	*p*-value
Elabela, pg/mL	1,874.56±4,757.59	280.24 (96.51-23,287.31)	5,409.94±9,261.34	596.98 (183.3-42,262.8)	0.087
Visfatin, ng/mL	18.41±6.53	2.92 (0.93-23.37)	15.23±5.87	15.83 (0.21-21.93)	0.002
Chemerin, ng/mL	3.33± 2.74	2.52 (0.68-12.91)	2.61±2.02	1.89 (0.41-8.16)	0.162

Table III. Correlation status of biomarkers.

	Pearson's or Spearman's correlation		
	R correlation coefficient	*p*-value	Result
Elabela – Chemerin	-0.348	0.047	Negative correlation. While the elabela increased, the chemerin decreased.
Elabela – Visfatin	-0.361	0.039	Negative correlation. While elabela increased, visfatin decreased.
Chemerin – Visfatin	0.415	0.016	Positive correlation. As chemerin increased, visfatin also increased.
Elabela – Platelet	0.343	0.050	Positive direction. As the elabela increased, so did the platelets.
Elabela – AST	-0.437	0.011	Negative direction. While elabela increased, AST decreased.

Aspartate transaminase (AST).

healthy control group and routinely used biomarkers such as WBC, CRP, PCT, in the diagnosis of ventilator-associated pneumonia (VAP). We evaluated whether ELA would be beneficial in prognosis. In our study, no statistically significant difference was found between serum ELA levels measured in the serum obtained at the time of diagnosis in 33 COVID-19 patients and the ELA values measured in the 30 healthy control group (p=0.087). The measurement of ELA values was not found to be significant in the diagnosis of COVID-19. Looking at the correlation between ELA and other parameters evaluated in our study, there was a positive correlation between ELA and chemerin (p=0.047), ELA and platelets (p=0.050), ELA and visfatin (p=0.039) and ELA and AST (p=0.011), and a negative correlation between ELA and AST (p=0.011).

Visfatin is a newly discovered adipocytokine largely secreted from adipose tissue and has been found[7] to play a role in many inflammatory events in the body. Since it can be synthesized from almost all visceral adipose tissue and peripheral mononuclear cells in the body and plays an active role in inflammatory processes, it is a biomarker that has been and continues to be frequently studied in a wide range of topics in the literature. When we examine visfatin and lung diseases, we see that it has been studied in disease groups such as chronic obstructive pulmonary disease (COPD), community-acquired pneumonia and lung cancer in the literature. We did not find any studies in the literature on COVID-19 patients. In the study by Liu et al[8], plasma visfatin levels were found to be significantly higher in COPD patients than in healthy controls. In the study by Göktepe et al[9], which included 30 patients with non-small cell lung cancer, 30 patients with COPD, and 30 healthy controls, serum visfatin levels were found to be lower in both lung cancer patients and COPD patients compared to the healthy control group. In our study, plasma visfatin levels measured in patients at diagnosis were significantly higher than visfatin levels in the healthy control group (p=0.002). This result shows that the measurement of visfatin levels may be meaningful in the diagnosis of COVID-19 disease. Looking at the correlation between visfatin and other parameters we evaluated in our study, a negative correlation was found between visfatin and ELA values (p=0.039). However, a positive correlation was found between visfatin and chemerin levels (p=0.016).

Chemerin is one of the newly discovered adipocytokines, which is mainly secreted from adipose tissue and skin, and has been shown[10-14] to play an active role in inflammatory processes with both pro- and anti-inflammatory properties. Göktepe et al[9] compared serum chemerin levels in lung cancer and COPD patients with a healthy control group. In this study, no significant difference was found between the serum chemerin values measured in the lung cancer and COPD patient group and the chemerin values in the healthy control group. In the study by Kukla et al[13], in which they compared the chemerin values measured in seventy COVID-19 patients with the healthy control group, chemerin values were found to be significantly lower than in the control group. Our study found no significant difference between the chemerin values measured during diagnosis in COVID-19 patients and those measured in the healthy control group (p=0.162). Therefore, we state that, unlike the study of Kukla et al[13], chemerin measurement does not help diagnose COVID-19. Looking at the correlation between chemerin and other parameters we evaluated in our study, a negative correlation was found between chemerin and ELA (p=0.047). However, a positive correlation was found between chemerin and visfatin levels (p=0.016).

Conclusions

In our study, it has been shown that the measurement of visfatin levels can be meaningful in the diagnosis of COVID-19 disease. Elabela and chemerin biomarkers do not help diagnose COVID-19. Larger studies are needed to show whether these three new inflammatory biomarkers, whose roles have been studied and continue to be studied in the diagnosis and prognosis of many diseases, will also help diagnose COVID-19.

Conflict of Interest

The authors declare there are no conflicts of interest.

Ethics Approval

The Non-interventional Ethics Committee of the Dicle University Medical Faculty approved the study (date: 20.05.2021, number 244).

Authors' Contributions

Tekin R and Mermutluoglu C study conception and design; Tekin R and Mermutluoglu C searched the literature; Mermutluoglu C wrote and edited the manuscript.

Availability of Data and Materials

The datasets are available from the corresponding author upon reasonable request.

Informed Consent

Patients consent forms were obtained.

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