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Effects of oxygen saturation on the hypoxia-inducible factor-1α, subfatin, asprosin, irisin, c-reactive protein, maresin-1, and diamine oxidase in diabetic patients with COVID-19

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Abstract. – OBJECTIVE: Oxygen is essential for living organisms that perform aerobic respiration since cells begin to die when humans and animals are deprived of oxygen. Oxygen saturation decreases and shortness of breath occurs in coronavirus (COVID-19) disease. Therefore, in this study, we aimed to determine the changes in hypoxia-inducible factor-1α (HIF-1α), subfatin, asprosin, irisin, C-reactive protein (C-RP), Maresin-1 (MaR-1), and diamine oxidase (DAO) molecules in diabetic patients with coronavirus according to their oxygen saturations.

PATIENTS AND METHODS: Participants were classified into 4 Groups of 22, including patients with oxygen saturation between 95% and 100% (Group I, control), between 80% and 85% (Group II), between 75% and 79% (Group III), and between 70% and 74% (Group IV). COVID-19 was diagnosed with PCR testing and 5 mL of blood was taken following the diagnosis. HIF-1α, subfatin, asprosin, irisin, MaR-1, and DAO values of the participants were measured with ELISA. Other parameters used in the study were obtained from the records of the patients.

RESULTS: When Group I was compared to Groups II, there was no significant change in Group II while HIF-1α, subfatin, asprosin, irisin, C-RP, and DAO counts had increased significantly in Groups III and IV. When the MaR-1 values were examined, they were reported to have decreased significantly in Groups III and IV ($p < 0.05$). Similarly, when Group II and Group IV were compared, HIF-1α, subfatin, asprosin, irisin, C-RP, and DAO values of the participants in Group IV had significantly increased while MaR-1 values had significantly decreased ($p < 0.05$). In the case of oxygen saturation decreasing below the critical value (70-74%) in patients with coronavirus, the release of HIF-1HIF-1α, subfatin, asprosin, irisin, C-RP, and DAO increased while the MaR-1 values decreased ($p < 0.05$).

CONCLUSIONS: Changes in these molecules in patients with coronavirus and diabetes according to their oxygen saturation suggested that they functioned as the "metabolic oxygen sensors" of the metabolism. Therefore, according to these data, it was predicted that these molecules had the potential to be used in the diagnosis and follow-up of diseases related to oxygen (such as asthma, and critical intensive care patients) in clinics in the future.

Key Words:
Oxygen saturation, Hypoxia-inducible factor-1α, Subfatin, Asprosin, Irisin, C-reactive protein, Maresin-1, Diamine oxidase, Diabetes mellitus, COVID-19.

Introduction

The SARS-CoV-2 virus has been one of the most fatal RNA viruses in the world since 2019. This virus belongs to the *Coronaviridae* family and the disease it causes has been named COVID-19 (CO=corona + VI=virus + D=disease + 19=2019= COVID-19) since it was reported to cause disease in humans in 2019[1,2]. This virus causes a wide range of infections including pneumonia in humans and causes decreased oxygen saturation, inflammation, impaired energy metabolism, and cytokine storm[3]. This study was conducted to determine the changes in hypoxia-inducible factor-1α (HIF-1α), subfatin, aspros-

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in, irisin, C-reactive protein (C-RP), Maresin-1 (MaR-1), and diamine oxidase (DAO) in patients with COVID-19 according to their oxygen saturations.

HIF-1α is a dimeric protein that plays a critical role in oxygen homeostasis. It is responsible for detecting and responding to changes in cellular oxygen concentration[4]. Also, dexmedetomidine promotes the recovery of renal function and reduces the inflammatory level in renal ischemia-reperfusion injury in rats through the PI3K/Akt/HIF-1α signaling pathway[5].

Most pleiotropic events are regulated by HIF-1α, and their levels increase at low oxygen concentrations[6]. It has been reported[7,8] that the mortality rate due to hypoxia increases in patients with COVID-19, especially in obese patients, due to the interaction between adipose tissue hypoxia and obstructive sleep apnea. Hypoxia develops due to severe lung injury and severe viral pneumonia in the majority of decompensated cases with COVID-19[9]. HIF-1α has been reported[10] to increase inflammatory responses to COVID-19 by provoking SARS-CoV-2 infection. In addition, HIF-1α reduces mitochondrial oxygen depletion and inhibits the tricarboxylic acid cycle (TCA) by the activation of pyruvate dehydrogenase kinase Ł 1[11]. In a study[12] on COVID-19, serum HIF-1α values were reported to be higher compared to the values of the control Group. Moreover, HIFs play a role in the pathogenesis of β-cell dysfunction and diabetes[4]. It has been reported[13] that the deletions of HIF-1α increase the complications of diabetes and worsen β cell functions. Improving glucose management in people with diabetes has been reported[14] to increase HIF-1α protein. Therefore, it is beneficial to determine whether HIF-1α values are correlated with subfatin, which is the mediator in glucose use, asprosin, and irisin, which is responsible for the destruction of fat[15,16].

Subfatin (Metrnl Protein) hormone blocks the release of inflammation-mediated molecules, and it is an important key player in glucose metabolism, which improves the intracellular insulin signal transduction[17]. This hormone (molecular weight -28 kDa) is also called adipokine (subfatin), cytokine (interleukin 39), and neurotrophic factor (cometin) depending on its function in different tissues[18]. The tissues where subfatin is most synthesized have been reported[19] to be the subcutaneous white adipose tissues of organisms. In addition to these tissues, it is also released from the liver, spleen, muscle, heart, thymus, forebrain, midbrain, hindbrain, and omental, perivascular, and interscapular adipose tissues[20]. There is not a complete consensus on how the subfatin changes due to diabetes. It increases due to diabetes according to a researcher[21] and decreases according to a study[22]. COVID-19 affects almost all biological systems[23]. As mentioned above, subfatin is synthesized and released in almost all biological tissues and it inhibits the release of inflammation- mediated molecules[20]. Therefore, there is a possible connection between the inflammation observed in COVID-19 and subfatin which needs to be investigated.

Asprosin is another conductor of the metabolism that acts together with the subfatin hormone. Asprosin is synthesized from white adipose tissue and controls the release of insulin and glucose[15]. Asprosin is encoded by two exons of the Fibrillin 1 (*FBN1*) gene (exon 65 and exon 66) and white adipose tissue is the main source of asprosin[24]. In a study[25], it was reported that the increase in asprosin in diabetes was independent of fasting glucose. *FBN1* mRNA is abundantly expressed in various organs, including the lung, and heart, and is a source of asprosin[26]. Since there is widespread lung involvement in cases of COVID-19, there may be a connection between asprosin and COVID-19[27]. There is a recent study[28] reporting that the amount of asprosin has decreased in patients with COVID-19.

In patients with COVID-19, food intake decreases due to loss of appetite[29]. Therefore, there may be a connection between irisin, which is responsible for fat destruction, and SARS-CoV-2 infection. Irisin is mainly synthesized from the skeletal muscle. It turns white adipose tissue into brown adipose tissue, causing fat destruction and weakening by causing heat energy to be released through couplings instead of ATP production. Irisin is synthesized and released into the circulation in almost all biological tissues except the skeletal muscle[16]. Studies[30,31] investigating the relationship between irisin, and diabetes are contradictory. Irisin increases due to diabetes according to a researcher[30] and decreases according to one other researcher[31].

C-reactive protein (“c” carbohydrate antibody of the capsule of pneumococcus) is a protein that increases in the blood during inflammatory reactions and is an acute phase reactant produced by liver and fat cells. It was discovered by Tillett and Francis[32] in 1930. C-RP has both proinflammatory and anti-inflammatory properties[33]. C-RP, which is a sensitive marker of systemic inflammation, has been reported[34] to increase in

patients with type 2 diabetes. C-RP could be used as indicator in the early diagnosis and evaluation of novel coronavirus pneumonia (COVID-19)[35].

MaR-1 is a molecule that is endogenously synthesized from docosahexaenoic acid (DHA)[36]. This anti-inflammatory molecule has a role in the elimination of acute inflammation of lung fibrosis, sepsis, obesity, and brain ischemia[37]. In addition, the administration of MaR-1 to animals causes the decrease of the proinflammatory cytokines secreted by macrophages[38]. The levels of MaR-1 in circulation also decrease due to diabetes[39]. Moreover, MaR-1 has been reported[40] to improve insulin resistance and reduce inflammation.

It may also be associated with the production of excess histamine in the body (mast cell-associated inflammation, allergy) associated with inflammation that causes the severe course of COVID-19 since histamine is a biological amine stored in mast cells and released when these cells are activated[41]. DAO is an enzyme responsible for the destruction of histamine[42]. There is a link between histamine intolerance and the development of prediabetes and diabetes[43]. It has been reported that histamine levels increase in diabetic conditions[44], and DAO levels decrease[45]. There are studies[46] reporting an increase in histamine levels in the circulation in cases with COVID-19.

Considering that the energy metabolism is affected, oxygen saturation decreases, inflammation increases, diffuse lung fibrosis occurs, and histamine release strongly increases according to the current data on COVID-19. Testing HIF-1α, subfatin, asprosin, irisin, C-RP, MaR-1, and DAO molecules together in patients with COVID-19 could be a guide for the course of COVID-19, and no studies have been conducted in the literature on this subject according to their oxygen saturations. In addition, many current studies[47-49] have indicated that it is not possible to diagnose and monitor any disease with a single biomarker. This is almost impossible in the case of SARS-CoV-2 infection, which is a very complicated disease affecting biological systems. Therefore, this study aimed to reveal the changes of HIF-1α, subfatin, asprosin, irisin, C-RP, MaR-1, and DAO molecules, which are interrelated in SARS-CoV-2 infection according to the oxygen saturation of the patients.

Patients and Methods

This study was conducted with the approval of Firat University Non-interventional Ethical Board dated July 4th, 2022 upon the meeting session (2022, 05/25) and numbered E-13281952-929. All patients had written informed consent and this prosses was performed in accordance with the Declaration of Helsinki. It included patients who presented to the Fethi Sekin City Hospital with certain complaints (cough, fever, respiratory distress, etc.) and who had similar body mass indeces (BMIs) and ages. Among the patients, 22 patients with an oxygen saturation between 95% and 100% were included in the healthy volunteer control Group (Group I, this Group consisted of individuals who came to our hospital for routine check-up examinations and did not have any medical conditions). In addition, 22 patients with COVID-19, whose oxygen saturations were between 80% and 85%, were included in Group II and 22 patients with COVID-19, whose oxygen saturations were between 75% and 79%, were included in Group III. Finally, 22 patients with COVID-19 and oxygen saturations between 70% and 74% were included in Group IV. As described before, 5 mL of blood samples were obtained from all patients[50].

Oxygen saturations of the participants were measured with Aircase Pulse Oximeter (model AC601, Hebei, China). They were centrifuged at 4,000 rpm and stored at -40 degrees Celsius until testing. In addition, the biochemistry parameters requested during the check-up or hospitalizations of the participants were obtained from the patient records. Type 2 diabetes was diagnosed according to the American Diabetes Association (ADA) criteria[51]. Moreover, medical histories and physical examinations of all patients with COVID-19 were performed, their sputum and blood tests were made for factor detection, and leukocyte, C-RP, and blood counts were measured. Radiological examinations (computed thoracic tomography, thoracic ultrasound, and chest radiography) were also performed. COVID-19 positivity was diagnosed by microbiology experts with Reverse-Transcriptase Polymerase Chain Reaction (RT-PCR) (Rotor-Gene Q, Qiagen Hilden, Germany) method[52].

ELISA Measurements

HIF-1α (Human HIF-1α ELISA Kit, catalog No.: 201-12-0423; Shanghai Sunred Biological Technology, Shanghai, China), DAO (Human DAO ELISA Kit, catalog No.: 201-12-0777; Shanghai Sunred Biological Technology, Shanghai, China), irisin (Human Irisin ELISA Kit,

catalog No.: 201-12-5328; Shanghai Sunred Biological Technology, Shanghai, China), Subfatin levels (Meteorin-like Protein) (Bioassay Technology Laboratory, catalog No.: E3941Hu Shanghai, China), and Asprosin (ELISA kit; Bioassay Technology Laboratory, catalog No.: E4095Hu Shanghai, China) counts were tested using the ELISA kit and ELISA method in accordance with the procedures of the manufacturer. MaR-1 was measured using the Enzyme-Linked Immunosorbent Assay, (SunRed, Biological Technology Co., Shanghai, China). Absorbances were read spectrophotometrically at 450 nm in the ChroMate Microplate Reader P4300 (Awareness Technology Instruments, Palm City, FL, USA) ELISA reader. Bio-TEK ELX50 (BioTek Instruments, Winooski, Vermont, USA) was used as an automatic washer in washing plates. The kit measurement range for subfatin was 0.05-15 ng/mL, with a minimum measurable level of 0.023 ng/mL. The measurement range of the kit for asprosin was 0.5-100 ng/mL and its minimum measurable level was 0.23 ng/mL. The measurement range of irisin was 0.157 ng/mL, 0.2-60 ng/mL, and the minimum measurable level was 0.157 ng/mL ng/mL. The measurement range of the MaR-1 kit was 0.10-1500 pg/mL. While the intra-assay CV value of the kits was <8%, the inter-assay CV value was <10%.

Statistical Analysis

Statistical analyses were performed on SPSS (SPSS Statistics for Windows, version 22.0. IBM Corp., Armonk, NY, USA) software. The Shapiro-Wilk test was used to evaluate the conformity of the variables obtained as continuous measurement values to normal distribution. According to the results of the test, the Student's *t*-test was used to compare the variables with normal distribution between the two independent Groups, and the Mann-Whitney U test was used in cases where the normal distribution was not achieved. Kruskal-Wallis' variance Analysis technique was used to compare multiple independent Groups. In cases where the difference between more than two independent Groups was found to be significant, the determination of the Groups that created the difference was determined by post-hoc multiple comparison tests. Demographic characteristics and Group comparisons were summarized as mean ± standard deviation. In our study, the level of statistical significance was taken as $p < 0.05$.

Results

The most common complaints of the patients admitted to our hospital at the time of admission were fever (34%) followed by cough (23%), which accounted for 57% of all admissions. There was no statistically significant difference between the age and body mass indices of all patients included in the study compared to the control Group ($p > 0.05$) (Table I). The comparison of biochemical laboratory parameters of the study Groups is presented in Table I. When the biochemical parameters were compared between the patient and control Groups, it was found that there was a statistically significant increase in the platelet, potassium, neutrophil, monocyte, iron, troponin, urea, and D-dimer values of Groups III and IV ($p < 0.05$). Leukocytes were the lowest in Group IV; however, monocyte levels had increased ($p < 0.05$). As the oxygen saturation of the Groups decreased, the levels of free iron, ferritin (contained iron increased). In addition, when the HIF-1α, subfatin, asprosin, irisin, C-RP, DAO, and MaR-1 counts were compared, they demonstrated a negative correlation and were statistically significant (r: -0.65, $p = 0.001$; r: -0.53, $p = 0.002$; r: -0.62, $p = 0.001$; r: -0.49, $p = 0.004$; r: - 0.67, $p = 0.001$; r: -0.48, $p = 0.004$, respectively).

When the HIF-1α values of Group I, Group II, Group III and Group IV were compared to each other, there was a statistically significant increase in Group III and Group IV compared to Group I and this increase was the highest in Group IV while no statistical significance was determined for Group II. When the HIF-1α values of Group II, Group III, and Group IV were compared among themselves, the HIF-1α values of Group IV were statistically significantly higher compared to Group II (Figure 1).

When the subfatin values of Group I, Group II, Group III, and Group IV were compared with each other, there was a statistically significant increase in Group III and Group IV compared to Group I, and this increase was the highest in Group IV while no statistical significance was determined for Group II. When the subfatin values of Group II, Group III, and Group IV were compared among themselves, the subfatin values of Group IV were statistically significantly higher compared to Group II (Figure 2).

When the asprosin values of Group I, Group II, Group III, and Group IV were compared with each other, Group III and Group IV demonstrated a statistically significant increase compared

Table I. Comparison of the demographic characteristics and biochemical parameters of the Groups by their oxygen saturations.

Parameters	Saturation (%)			
	Group I (96.95)	Group II (84.13)	Group III (77.77)	Group IV (72.22)
Female/Male	11/11	9/13	10/12	9/13
Age (year)	50.27 ± 2.83	52.68 ± 3.35	50.09 ± 4.05	51.63 ± 3.06
BMI (kg/m^2)	23.00 ± 1.27	26.00 ± 1.97^{a}	28.00 ± 3.32^{b,e}	31.00 ± 3.97^{d,g,i}
Glucose (mg/dL)	86.40 ± 5.60	134.05 ± 13.91	139.31 ± 16.35	144.59 ± 19.95
D-dimer (µg/mL)	0.82 ± 0.04	0.84 ± 0.11	1.66 ± 0.20^{b,f}	2.02 ± 0.21^{d,g,j}
Creatine (mg/dL)	0.78 ± 0.71	0.81 ± 0.64	0.84 ± 0.51c	0.86 ± 0.57^{d,h}
Ferritin (µg/L)	139.22 ± 7.69	183.90 ± 12.21^{a}	207.27 ± 19.18^{b,f}	269.22 ± 23.95^{d,g,j}
Troponin (ng/dL)	0.00 ± 0.00	7.26 ± 0.79^{a}	8.39 ± 0.39^{b,f}	12.91 ± 0.70^{d,g,j}
Urea (mmol/L)	36.93 ± 3.11	43.80 ± 2.73^{a}	43.68 ± 2.38^{b}	46.66 ± 2.24^{d,g,j}
Total Bilirubin (mg/dL)	0.52 ± 0.03	0.57 ± 0.05^{a}	0.65 ± 0.03^{b,f}	0.67 ± 0.05^{d,g}
WBC (×10^3 cells/µL)	6.57 ± 0.34	8.61 ± 0.64^{a}	8.95 ± 0.33^{b,e}	10.80 ± 1.35^{d,g,j}
Neutrophil (×10^3 cells/µL)	5.85 ± 0.32	6.81 ± 0.51^{a}	6.02 ± 0.80^{b}	6.11 ± 0.27^{d,g,j}
Lymphocyte (×10^3 cells/µL)	1.34 ± 0.19	1.28 ± 0.23	1.26 ± 0.26	1.26 ± 0.24
Monocyte (×10^3 cells/µL)	0.41 ± 0.07	0.58 ± 0.07^{a}	0.65 ± 0.06^{b,f}	0.68 ± 0.05^{d,g}
Hemoglobin (g/dL)	13.90 ± 0.34	12.96 ± 0.76^{a}	12.80 ± 0.58^{b}	12.29 ± 0.42^{d,g,j}
Na (mmol/L)	141.81 ± 13.73	140.23 ± 12.78	137.25 ± 13.78^{b,f}	132.04 ± 13.30^{d,g,j}
Cl (mmol/L)	103.56 ± 14.72	101.58 ± 13.38	104.62 ± 14.57^{e}	103.28 ± 12.31^{h}
K (mmol/L)	4.18 ± 0.13	4.83 ± 0.43^{a}	5.13 ± 0.21^{b,f}	5.52 ± 0.22^{d,g,j}
Fe (µmol/L)	42.3 ± 1.13	68.40 ± 1.99^{a}	67.91 ± 2.75^{b}	72.34 ± 1.90^{d,g,j}

Group I: Control. BMI: Body mass index. WBC: White blood cells. [a]Group I *vs*. Group II ($p < 0.01$). [b]Group I *vs*. Group III ($p < 0.01$). [c]Group I *vs*. Group III ($p < 0.05$). [d]Group I *vs*. Group IV ($p < 0.01$). [e]Group II *vs*. Group III ($p < 0.05$). [f]Group II *vs*. Group III ($p < 0.01$). [g]Group II *vs*. Group IV ($p < 0.01$). [h] Group II *vs*. Group IV ($p < 0.05$).[i]Group III *vs*. Group IV ($p < 0.05$). [j]Group III *vs*. Group IV ($p < 0.01$).

to Group I and this increase was the highest in Group IV while no statistical significance was determined for Group II. When the asprosin values of Group II, Group III, and Group IV were compared among themselves, the asprosin values of Group IV were significantly higher compared to Group II (Figure 3).

When the irisin values of Group I, Group II, Group III, and Group IV were compared with each other, there was a statistically significant increase in Group III and Group IV compared to Group I, and this increase was the highest in Group IV while no statistical significance was determined for Group II. When the irisin values of Group II, Group III, and Group IV were compared among themselves, the irisin values of Group IV were reported to be significantly higher compared to Group II (Figure 4).

When the C-RP values of Group I, Group II, Group III, and Group IV were compared among each other, Group III and Group IV showed a significant increase compared to Group I, and this increase was the highest in Group IV. Group II was not statistically significant. When the C-RP

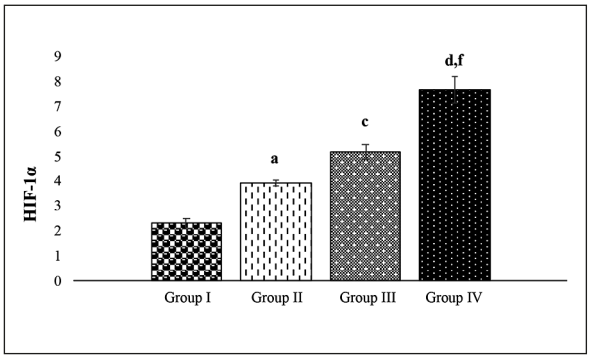

Figure 1. Comparison of HIF-1α values in Groups by their oxygen saturations.

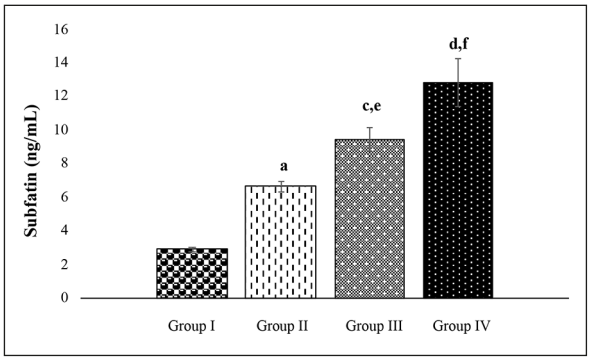

Figure 2. Comparison of subfatin values in Groups by their oxygen saturations.

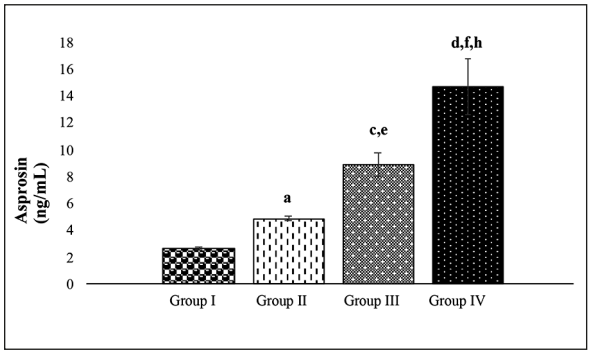

Figure 3. Comparison of asprosin values in Groups by their oxygen saturations.

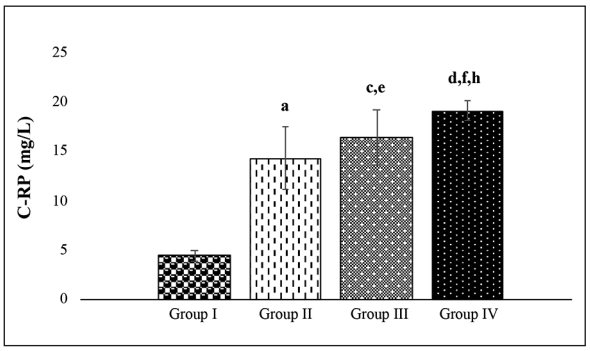

Figure 5. Comparison of C-RP values in Groups by their oxygen saturations.

values of Group II, Group III, and Group IV were compared among themselves, the C-RP values of Group IV were significantly higher than Group II (Figure 5).

When the MaR-1 values of Group I, Group II, Group III, and Group IV were compared with each other, Group III and Group IV demonstrated a statistically significant decrease compared to Group I, and this decrease was the highest in Group IV while no statistical significance was determined for Group II. When the MaR-1 values of Group II, Group III, and Group IV were compared among themselves, the MaR-1 values of Group IV were significantly lower compared to Group II (Figure 6).

When the DAO values of Group I, Group II, Group III, and Group IV were compared with each other, there was a statistically significant increase in Group III and Group IV compared to Group I, and this increase was the highest in Group IV while no statistical difference was observed for Group II. When the DAO values of Group II, Group III, and Group IV were compared among themselves, the DAO values of Group IV were statistically significantly higher than Group II (Figure 7).

Discussion

SARS-CoV-2 has been on the agenda in the health community for more than two years since it affects many biological systems and organs, causes deaths, and it has been reported[53] that respiratory distress syndrome (shortness of breath) has the most significant effect; however, the metabolic molecules affected in biological systems due to this syndrome have not yet been fully revealed. Under hypoxic conditions, energy metabolism (glucose metabolism) in the cell is regulated by HIF (oxygen sensitivity mechanism)[54]. The regulation of energy metabolism in the organism is under strict control by a large number of adipokine-derived peptide-structured hormones (asprosin causes glucose release from the liver, while subfatin mediates the regula-

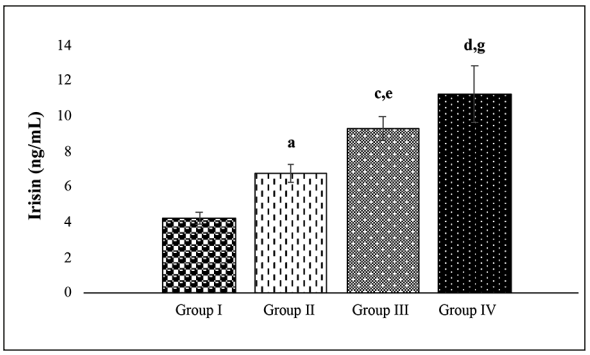

Figure 4. Comparison of irisin values in Groups by their oxygen saturations.

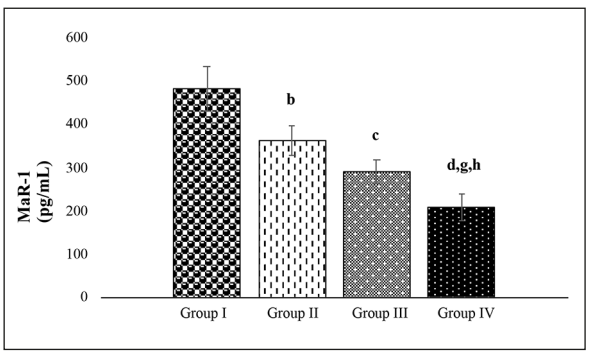

Figure 6. Comparison of MaR-1 values in Groups by their oxygen saturations.

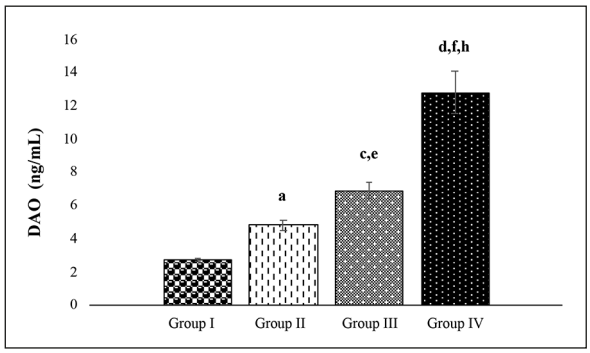

Figure 7. Comparison of DAO values in Groups by their oxygen saturations.

tion of the physiological effects of insulin)[19,55]. All infections, including SARS-CoV-2 infection, cause inflammation[56]. The most important classical marker of inflammation due to infections is the C-RP molecule[57], and the MaR-1 molecule has been reported[58] to be an important marker of inflammation in recent years. In this study, the changes of HIF-1α, asprosin, subfatin, irisin, MaR-1, C-RP, and DAO molecules according to oxygen saturations of patients with COVID-19 were investigated for the first time.

In oxygen-dependent organisms, oxygen deficiency tends to reduce oxygen use and energy need in tissues and leads to the synthesis of transcriptional factors that enable its adaptation to hypoxic conditions[59]. For example, HIFs are transcriptional factors that respond to the decrease in oxygen levels[60]. In this study, it was found that the amount of HIF-1α increased as oxygen saturation decreased in patients with diabetes. The levels of HIF-1α were reported to have increased in studies[14] on patients with diabetes. In this study, the increase in HIF-1α levels in patients with COVID-19 increased depending on the decrease of oxygen saturations rather than high circulating glucose because there was no significant difference between the glucose amounts of diabetic Groups. In addition, it was previously reported[61] that cellular HIF-1α levels increased in organisms due to hypoxia caused by infection. When metabolic hypoxia due to SARS-CoV-2 occurs, cells might increase HIF-1α synthesis to save themselves from oxygen starvation. Increased HIF-1α reduces mitochondrial oxygen depletion and inhibits the TCA by activation of pyruvate dehydrogenase kinase 1[11]. At the end of these metabolic events, tissues and cells adapt to low oxygen levels (hypoxia) while activating a large number of pathways, including iron and glucose metabolism[59]. In short, these data indicate that HIFs play an important regulatory role in inflammation. For example, HIFs not only regulate glycolytic energy production in macrophages, but also optimize innate immunity, control proinflammatory gene expression, mediate the killing of pathogens, and can affect cell migration[62].

Moreover, it was found in the present study that the subfatin values increased as the oxygen saturation decreased in patients with diabetes and coronavirus. Subfatin is produced by monocytes, adipocytes, and skeletal muscle[63]. Severe muscle damage occurs in COVID-19 disease[64]. This muscle damage may have caused excessive subfatin release and thus subfatin accumulation in the circulation. In addition, subfatin may have increased in circulation as a result of a compensatory mechanism to reduce inflammation that occurred in the skeletal muscle due to COVID-19. Another reason for the increase in subfatin values due to the decrease in oxygen saturations may have been the increase in monocyte values due to COVID-19 infection since monocytes are an important subfatin production factory[63]. Apart from all these mechanisms, the subfatin values may have increased in order to closely control the changing energy molecules (such as glucose and fats) due to COVID-19 as subfatin is a hormone that plays a role in glucose homeostasis[17]. Since this is the first study to compare how subfatin changes according to oxygen saturations, we cannot compare our results. It needs to be confirmed by an independent research laboratory in the future.

In this study, asprosin values were found to increase as oxygen saturation decreased in patients with diabetes and coronavirus. In a study[28] conducted on patients with COVID-19, the asprosin values were reported to have decreased, which was contradictory to the results of the current study. Asprosin is a peptide hormone. Since they break down quickly when taken into biochemical tubes without a protease inhibitor[65], they are detected in low amounts when measured. We believe that this was the potential reason why the results of the current study and the previous study[28] were contradictory. In addition, asprosin is also a molecule that mediates glucose release from the liver[55]. Asprosin levels may have increased in the circulation to contribute to meeting the energy demand of the organism. In studies[25] conducted with diabetic patients, asprosin levels were reported to have increased, and these results were

consistent with the results of the current study. In addition, as in the mechanisms mentioned above, the increase in asprosin in this study was associated with a decrease in the oxygen saturation of the patients since the asprosin values increased as the oxygen saturation decreased.

In this study, irisin levels were found to increase as oxygen saturation increased in diabetic patients with coronavirus. The increased irisin in the circulation in our study on COVID-19 may be that the irisin found in the heart muscle may have contributed to the serum pool when they were released as a result of the damage to the heart muscle[66]. This may have also been due to an increase in cardiac damage caused by viral myocarditis[67]. In addition, since irisin is a molecule with anti-inflammatory activity, it may have increased to eliminate inflammation in patients with COVID-19[68]. In cases of infection, weight loss due to loss of appetite may also be associated with the destruction of fats of irisin, whose synthesis increases due to infection.

As oxygen saturation decreased, the C-RP value increased in patients with diabetes and coronavirus. Some studies[34,69-71] show that C-RP increases significantly in the first stage of COVID-19 infection. In this study, C-RP values increased significantly as oxygen saturation decreased. It was believed that this increase in C-RP values as oxygen saturation decreased triggered inflammation due to metabolic oxygen deficit; and therefore, C-RP could increase in diabetic patients with COVID-19.

MaR-1 is another molecule that plays a role in inflammation. This molecule is a powerful anti-inflammatory with the capacity to prevent inflammation by reducing neutrophil infiltration and increasing the phagocytic activity of macrophages[37]. In our study, MaR-1 levels were also investigated for the first time in SARS-CoV-2 infection according to oxygen saturations. As oxygen saturations decreased, a significant decrease was observed gradually in the levels of MaR-1. SARS-CoV-2 infection increases inflammation[72]. In this study, it was theoretically expected that endogenous production of MaR-1 in the organism would increase in the inflammatory process since infection would cause an increase in macrophages[73]. The increase of macrophages leads to the production of MaR-1; and furthermore, the human neutrophil may interact with platelets to increase the production of endogenous MaR-1 upon the effect of 12-lipoxygenase 1. As in this study, there is an increase in platelet counts due to COVID-19. Therefore, while it was expected that the increase in platelet amounts would cause an increase in MaR-1 production; on the contrary, MaR-1 amounts were reported to have decreased. We believed that the possible cause of the decrease in MaR-1 values in this study was that it was metabolically consumed to eliminate inflammation. Therefore, as the oxygen saturation of the patients decreased, their inflammation increased (C-RP increase was important evidence in our study); and accordingly, this anti-inflammatory molecule may have decreased to eliminate inflammation. Previously, MaR-1 values were reported[74] to have decreased in cases of inflammation.

In this study, DAO levels were found to increase as oxygen saturation decreased in patients with diabetes and coronavirus. These data indicated that the increase in DAO levels as oxygen saturation decreased in COVID-19 was one of the main parameters showing the metabolic oxygen demand of the patient and inflammation. Mast cells are histamine production factories[75]. Histamine increases in COVID-19 infection[76]. The DAO levels may have increased to eliminate histamine in COVID-19 infection as DAO is an enzyme that plays a role in the elimination of histamine[77]. DAO amounts were reported to decrease due to diabetes, and these DAO data were not consistent with the current study. Proliferation has found lower levels of histamine-degrading DAO enzymes in diabetic rats[78]. Nevertheless, the increase in DAO in patients with diabetes and COVID-19 observed in this study was associated with the low oxygen saturation of the patients rather than high circulating glucose. Histamine levels could not be measured in this study. However, in a previous hypothesis and a study[79], it was reported that the use of antihistamine had a role in the control of COVID-19 infection. Using antihistamines in COVID-19 infection can contribute to the prevention of shortness of breath in patients as histamine is a molecule that also causes shortness of breath[79,80]. As viral diseases cause histamine release by making mast cells sick, the use of antihistamines in the treatment of these diseases may be important in the future[79].

In addition, when the patient and control Groups were compared in terms of platelet, potassium, monocyte, iron, troponin, and D-dimer values in the study, the increase of these molecules was significant, especially in Groups III and IV. The increase in these molecules due to the decrease in oxygen saturation was consistent with the previously recorded results[81,82] in pa-

tients with COVID-19. These changes in patients with COVID-19 in terms of platelet, potassium, monocyte, iron, troponin, and D-dimer values indicate that it is an important catastrophic disease in which the general homodynamic structure of the organism is impaired.

In this study, it was found that as the oxygen saturation decreased in patients with COVID-19, the free iron, ferritin (contained iron) levels increased. High ferritin (stored iron) may be used to eliminate free iron in circulation. It was reported in previous studies[83,84] that the level of free iron and ferritin in the circulation of patients with COVID-19 increased, and this is compatible with the current study. In patients with COVID-19, the possible reason for reporting high free iron and ferritin may be that SARS-CoV-2 seizes the porphyrin by attacking the 1-beta chain of hemoglobin, separating the iron molecule, and pumping iron into the circulation[85]. In addition, this free iron pumped into the circulation may be one of the underlying mechanisms of inflammation of lung macrophages; in other words, the ground-glass image, in patients with COVID-19[86]. Moreover, it is an indicator of hemoglobin (Hb), which has lost its ability to carry excess iron and oxygen in circulation. It is suggested that patients with COVID-19 compensate this situation by increasing the rate of Hb production. Therefore, hyperferritinemic syndrome SARS-CoV-2 is an indicator of viral infection[87]. In addition, the monocytosis we reported in our patients may be due to the tendency to produce macrophages by surrounding the iron molecules of the body. The decrease in circulating leukocytes and increased neutrophils reported in this study may be due to SARS-CoV-2 invasion as a result of bone marrow suppression or peripheral destruction in the early stages of infection[88]. Hence, this did not exceed the lower limit to categorize as leukopenia or neutropenia, and these parameters were studied in blood samples of patients with breathing difficulties as soon as they were diagnosed with COVID-19. Moreover, lymphopenia may be caused by the differentiation of white blood cells towards monocyte formation[89].

As in all studies, there were some limitations in this study. First of all, the number of participants in our study was low. In addition, we believe that it is important to measure histamine in patients with COVID-19. Although DAO measurement indirectly provides information about histamine values, as in this study, we think that it is beneficial to measure it together in the future.

Conclusions

As a result, this study had the limitations mentioned above; however, the fact that HIF-1α, subfatin, asprosin, irisin, C-RP, and DAO values increased while MAR-1 decreased as the oxygen saturations decreased was revealed for the first time in this study. The changes observed in these molecules as oxygen saturation decreased may be an indicator of hyperinflammation. In addition, the changes observed in these molecules were independent of glucose concentrations and associated with decreased oxygen saturations because there was no significant difference between the glucose amounts of diabetic Groups. Measuring these molecules in the future can guide clinicians on the course of viral infections. Moreover, the administration of MaR-1, which has anti-inflammatory properties, in diabetes accompanied by COVID-19 may contribute to the improvement of the clinical course of patients.

Conflict of Interest
The Authors declare that they have no conflict of interests.

Ethics Approval
This study was approved by the Firat University Non-interventional Ethical Board.

Informed Consent
All patients provided written informed consent.

Authors' Contribution
Zuhal Karaca Karagoz, Suleyman Aydin: contributed to study conception, design, collect to data, data interpretation, preparing the draft manuscript, and final approval of the version to be published. Suleyman Aydin, Zuhal Karaca Karagoz: contributed to study conception, design, to data analysis, data interpretation, preparing the draft manuscript, and final approval of the version to be published.

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Availability of Data and Materials
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