Original Article

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Serum FGF-21 Levels During COVID-19 Infection Recovery Period

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Abstract

Aim: Mitochondrial dysfunction causes oxidative stress, which triggers the release of proinflammatory cytokines, which play an important role in the immune response. One of these cytokines, fibroblast growth factor-21 (FGF-21), has demonstrated an increase in its level in severe coronavirus disease-2019 (COVID-19) infection. In this context, this study aimed to investigate whether FGF-21 can be used in the follow-up of COVID-19 infection.

Methods: This study was conducted as a cross-sectional design between January 1, 2022, and December 31, 2022. This study included women and men over 18 years old who had recovered from the COVID-19 infection (n=27). The data regarding hospitalization place (internal medicine ward, internal medicine ward + intensive care unit), comorbidities, vital signs, acute respiratory distress syndrome development, and applied treatments were obtained from hospital records. Fibroblast growth factor-21 levels were specifically studied for this study.

Results: The FGF-21 level was found to be 254 pg/mL at the beginning of the study and increased to 454 pg/mL at the end of the study. The difference was found to be statistically significant (p=0.004).

Conclusion: Considering the increasing level of FGF-21 compared to the beginning of the infection, it is thought that FGF-21 plays a role in the healing process in the COVID-19 infection.

Keywords: Fibroblast growth factor-21, COVID-19, acute respiratory distress syndrome, risk factors, hospitalization, and intensive care unit

Introduction

The fibroblast growth factor (FGF) family comprises polypeptides consisting of five paracrine subfamilies and one endocrine subfamily. Paracrine subfamilies play important roles during embryonic development. The endocrine subfamily members are FGF-19, FGF-21, and FGF-23, which are hormones that help regulate the metabolism of bile acid, lipids, glucose, vitamin D, and minerals. They act by binding to tyrosine kinase receptors (1). One of the FGFs is FGF-21. Fibroblast growth factor-21 levels increase in cases of inflammation such as obesity, metabolic syndrome, and stress. This increase protects the organism from the effects of inflammation and oxidative stress. It is known that FGF-21 levels increase in the early stages of illnesses and are related to healing. Li et al. (2) studied FGF-21's effects on the post-myocardial infarction healing term and the development of fibrosis and reported that FGF-21 levels increased during the healing process.

In addition, FGF-21 increases in cases of acute inflammation, such as bacterial infections. FGF-21 mice were more likely to die because of endotoxemia (3). The observation of more deaths after lipopolysaccharide injection in mice without FGF-21 suggested that FGF-21 protects the organism against sepsis. A possible underlying cause is that FGF-21 inhibits macrophage activation (4). It is thought that a high FGF-21 level creates a protective mechanism against sepsis. However, it was determined that the increase during bacterial infection occurs in the late stage of inflammation (5). Similarly, FGF-21 levels change during viral infection, and it helps to follow-up on the infection (6).

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Coronavirus disease-2019 (COVID-19) is an important viral infection that caused a global pandemic. Because it can be asymptomatic or mild, it can also lead to pneumonia, acute respiratory distress syndrome (ARDS), respiratory failure, multiple organ failure, and even death. The risk of hospitalization and death is higher in individuals with DM, obesity, and cardiovascular disease (7). The inflammatory response during the disease is the underlying cause of this condition. The immune response enters a vicious cycle when a cytokine storm adds to this low-grade inflammation (8).

In COVID-19 infection, RNA and proteins belonging to the virus settle in the mitochondria of the host and disrupt the functioning of the mitochondria, which have an important role in the immune response. Mitochondrial dysfunction leads to oxidative stress, which leads to the release of proinflammatory cytokines, which have an important role in the immune response. Fibroblast growth factor-21, also known as cytokines, is one of these cytokines, and its level has been shown to increase in severe COVID-19 infection (9). In this context, this study aimed to investigate whether FGF-21 can be used in the follow-up of COVID-19 infection.

Materials and Methods

Compliance with Ethical Standards

The ethical approval was obtained from the Tokat Gaziosmanpasa University Faculty of Medicine, Clinical Research Ethics Committee (approval no.: 21-KAEK-165, date: 01.07.2021).

Study Design

This study was conducted as a cross-sectional design between January 1, 2022, and December 31, 2022. Women and men who were over 18 years old and recovered from the COVID-19 infection were included in this study. Pregnant women, lactating women, those younger than 18 years of age, and substance abusers were excluded from the study. Forty hospitalized patients were reviewed, and 32 were included in this study. Five individuals died during the study period, and the process continued in 27 patients (Figure 1). They reported complaints of cough, fever, and lower respiratory tract infection and were diagnosed with COVID-19 pneumonia on the basis of the results of polymerase chain reaction and lung tomography at admission. Anamnesis, demographic data, and routine laboratory results were obtained from the hospital database. Oxygen saturation, blood pressure, fever, and pulse values of the patients were measured daily.

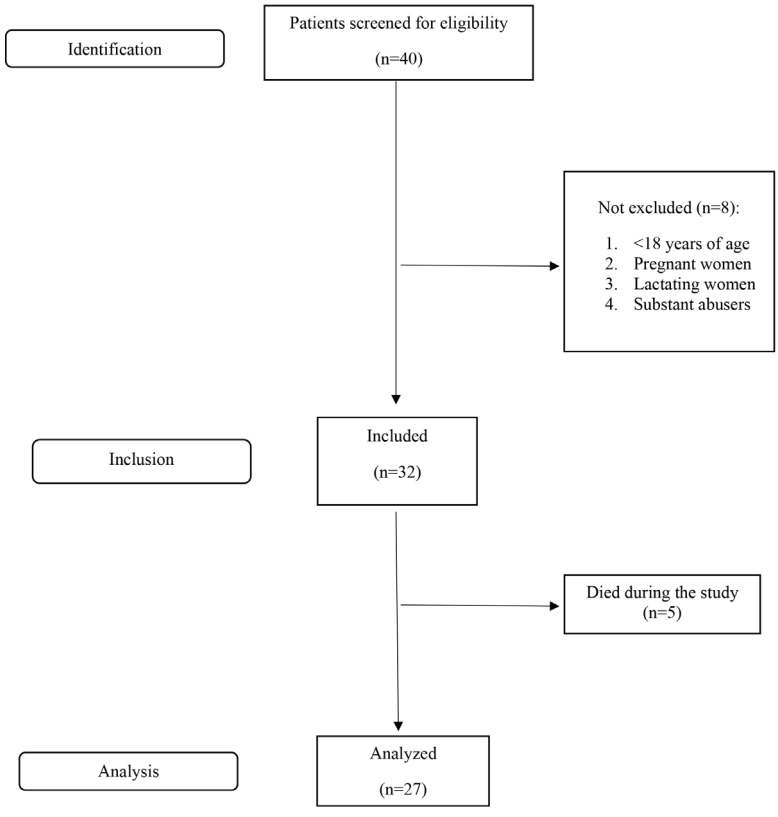

Figure 1. Patient flow diagram

Test values, which were routinely sent from the patients, such as hemogram, fasting plasma glucose (FPG), lipid profile [total cholesterol, low-density lipoprotein-cholesterol, high-density lipoprotein (HDL)-cholesterol, triglyceride], C-reactive protein (CRP), D-dimer, ferritin, and kidney and liver function tests, were obtained from the hospital database for the days of hospitalization and discharge. Serum specimens were analyzed for FGF-21 levels on the days of hospitalization and discharge.

Patients with FPG ≥126 mg/dL and HbA1c level ≥6.5 were considered diabetic, and those with FPG 100-125 mg/dL and HbA1c level 5.7-6.4 were considered pre-DM.

Collection of Blood Samples

Cells from blood samples were rapidly separated using a centrifuge at 3000 g for 10 min and then stored at 80 °C until analysis.

FGF-21 Measurements

FGF-21 levels were measured using an enzyme-linked immunosorbent assay (ELISA) kit (Elabscience Biological Technology Company, Cat. No. E-EL-H0074, USA) following the manufacturer's instructions. The measurement range of the FGF-21 ELISA kit was 31.25-2000 pg/mL. After the serum samples were diluted by X^2 using a dilution buffer, two wells were studied for each sample. Plates were scanned using a Thermo Scientific microplate reader (USA) at 450 nm. Fibroblast growth factor-21 levels were calculated in pg/mL using the 4-parameter standard curve. The final concentrations were determined by multiplying the results by the dilution factor.

Statistical Analysis

Statistical analyses were conducted using IBM SPSS for Windows Version 24.0 software. Numerical variables are summarized as mean ± standard deviation (SD) and median (minimum-maximum), whereas categorical variables are expressed as numbers and percentages. The differences between the groups in terms of categorical variables were analyzed using the χ^2 test or Fisher's exact test. The Kolmogorov-Smirnov test, histograms, SD/mean ratios, skewness, and kurtosis were used to determine if the numerical variables were distributed normally. The homogeneity of variance was tested using the Levene test. The t-test was used for normally distributed parameters, and the Mann-Whitney U test was used for non-normally distributed parameters. Pearson's correlation analysis was used to determine the relationships between the parameters. The significance level was set at $p<0.05$

Results

This study involved 27 patients. Only 7 of the patients were followed up in the general ward, whereas the remaining 20 patients who developed acute respiratory distress syndrome (ARDS) were followed up in the ICU and were taken to the general ward when there was no need for the ICU anymore (Table 1). Methylprednisolone, favipiravir, proton pump inhibitors, antibiotics (piperacillin-tazobactam or moxifloxacin), and low-molecular-weight heparin were administered to the patients for treatment.

Table 2 compares the patients' vital signs and laboratory parameters from the first to the last days of hospitalization. When compared to the moment of admission, there was an improvement in oxygen saturation, as well as a significant increase in lipid parameters (blood urea nitrogen, alanine aminotransferase, hemogram, and FGF-21), and a significant decrease in creatinine and CRP at the moment of discharge.

A correlation analysis was performed between the change in the FGF-21 level (ΔFGF-21) and the change in other numerical data. There was a significant negative correlation between HDL change (Table 3), whereas there was no correlation between other parameters and ΔFGF-21.

Twenty of the patients were followed in the ICU, whereas seven patients were followed in the ward. Considering glucose metabolism, although there were more DM and preDM patients and fewer normal ones in the ICU (p=0.027), it was observed that the distribution was not affected after COVID-19 infection (Table 4). It was thought that being diabetic or pre-DM increased the risk of hospitalization in the ICU.

Table 1. Basal characteristics of the patients

Parameter	Data
Age, mean ± SD	56.8±16.3 (34-93)
Gender (F/M) n (%)	14 (51.9)/13 (48.1)
Systemic disease, n (%)	
HT	3 (11)
ASHD	2 (0.7)
RA	1 (0.3)
DM	13 (48.1)
preDM	8 (29.6)
Patient's ward, n (%)	
General ward	7 (25.9)
General ward + ICU	20 (74.1)
Number of patients receiving pulse steroids during hospitalization, n (%)	26 (96.3)
Pulse steroid dose (mg), mean ± SD	119.25±103.32
Number of patients who developed ARDS, n (%)	23 (85.2)
Number of patients with antibiotic indication, n (%)	24 (88.9)

SD: Standard deviation, F/M: Female/Male, HT: Hypertension, ASHD: Atherosclerotic heart disease, RA: Rheumatoid arthritis, DM: Diabetes mellitus, ARDS: Acute respiratory distress syndrome, ICU: Intensive care unit

Table 2. Comparison of parameters in all patients according to the beginning and end of COVID			
	At the beginning	**At the end**	**p-value**
Fever (°C)	36.2 (35.8-37.9)	36 (36-36.7)	0.143
Heartbeat rate (beat/min)	83.6±15.2	84±12.8	0.903
Systolic pressure (mmHg)	112.6±13.4	114.8±13.4	0.471
Diastolic pressure (mmHg)	69.2± 10.3	70.3±8.5	0.502
Saturation	**94.6±3.4**	**96.7±1.7**	**0.005***
FPG (mg/dL)	138 (84-369)	115 (82-439)	0.885
HbA1c	6 (5.4-11.9)	6 (5.3-11.9)	0.066
Triglyceride (mg/dL)	**115 (35-386)**	**180 (83-426)**	**0.001***
HDL (mg/dL)	**41.9±14.3**	**46.7±12.1**	**0.041***
LDL (mg/dL)	**103.2±30.1**	**121.1±31.9**	**0.001***
Total cholesterol (mg/dL)	**159.3±34.8**	**178.7±39.8**	**0.048***
Creatinine (mg/dL)	**0.97 (0.47-6.70)**	**0.83 (0.34-5.8)**	**0.025***
BUN (mg/dL)	**32 (15-177)**	**48 (96-160)**	**0.022***
ALT (U/L)	**20 (10-82)**	**38 (10-199)**	**0.003***
AST (U/L)	28 (9-102)	19 (10-106)	0.160
CRP (mg/L)	**49.88 (3.56-219)**	**2.56 (0.26-142)**	**<0.001***
D-dimer (mcg/mL)	0.37 (0.04-8.46)	0.28 (0-6.94)	0.279
Ferritin (mcg/L)	229 (32-1629)	158 (14.1-7738)	0.254
Fibrinogen (mg/dL)	479.2±118.2	500.5±180.2	0.810
Hb (g/dL)	12.28±3.2	12.69±2.1	0.328
Leucocyte (10^3/μL)	**6550 (1760-14250)**	**9680 (1677-25220)**	**0.024***
Lymphocyte (10^3/μL)	**1010 (250-8520)**	**2240 (720-3610)**	**<0.001***
Neutrophil (10^3/μL)	**5098.1±2858**	**7639.6±3451.4**	**0.003***
Platelet (10^3/μL)	**232000 (123000-554000)**	**347000 (148000-659000)**	**<0.001***
FGF-21 (pg/mL)	**254 (32-861)**	**454 (33-1888)**	**0.004***

*: Statistically significant
COVID: Coronavirus disease, FPG: Fasting plasma glucose, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, PreDM: Pre-diabetes mellitus, DM: Diabetes mellitus, BUN: Blood urea nitrogen, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CRP: C-reactive protein, Hb: Hemoglobin, FGF-21: Fibroblast growth factor-21

Table 3. Correlation between ΔFGF and variation in numerical parameters		
	R-value	**p-value**
ΔHDL (mg/dL)	-0.424	0.044*

*: Statistically significant
FGF: Fibroblast growth factor, HDL: High-density lipoprotein

Table 4. Relationship between the ICU and glucose metabolism			
	Only ward (n=7)	**Ward + ICU (n=20)**	**p-value**
Glucose metabolism (before COVID), n (%) Normal PreDM DM	 4 (57.1) 2 (28.6) 1 (14.3)	 2 (10) 6 (30) 12 (60)	**0.027*** **All subgroups were statistically significantly different (post-hoc analysis)**
Glucose metabolism (after COVID), n (%) Normal PreDM DM	 2 (28.5) 4 (57) 1 (14.5)	 2 (10) 5 (25) 13 (65)	0.079

*: Statistically significant
ICU: Intensive care unit, COVID: Coronavirus disease, PreDM: Pre-diabetes mellitus

Discussion

All patients recovered from the infection and were discharged. Therefore, there was a positive change in the parameters, indicating inflammation. The fact that all the patients recovered and the FGF-21 levels increased compared with the onset of infection indicates that FGF-21 metabolism increases during the recovery period of COVID-19 infection. Following the COVID infection, there was an increase in all lipid parameters. Additionally, there was an increase in HDL. Lipid metabolism is active during the viral infection process (10). It meets the need for lipids, which increases because of viral replication. In the literature, it has been reported that the lipid pathway plays an important role in the progression of viral infection, that there is an increase in activity of this pathway during the infection process, and that trying to break this pathway with anti-lipid drugs such as statins contributes to the infection process (11,12). Furthermore, the increase in the lipid profile in this study can be explained by this. The fact that patients had to be administered steroids may also be a factor in this increase.

Fibroblast growth factor-21 levels are high in obese people with dyslipidemia and diabetes. It has been identified as a potential biomarker for metabolic syndrome and diabetes (13,14). In a study conducted by Gawlik et al. (15), FGF-21 levels were higher than normal in patients with type 2 diabetes, whereas a negative correlation with HDL was found in these patients. A negative correlation between FGF-21 and HDL was also observed in another study in which FGF-21 levels were investigated in individuals with a high metabolic risk like type 2 DM, metabolic syndrome, atherosclerosis, and smoking (16). We also found a negative correlation between FGF-21 and HDL levels in our study, which supports the literature (Table 3).

In this study, DM and preDM were detected more frequently at discharge than at disease onset. Besides, the need for the ICU was observed more in DM and preDM patients. There was no relationship between FPG, HbA1c, and FGF-21 levels.

Steroids, or glucocorticoids, are drugs of common use. Both benefits and harms are associated with steroids. Some of the negative effects include osteoporosis, diabetes, dyslipidemia, cardiovascular disorders, and neurological dysfunction. Hyperglycemia is a frequently occurring condition. Lipolysis and proteolysis promote gluconeogenesis in the liver, which generates a substrate for gluconeogenesis in muscle and adipose tissue. This process inhibits insulin synthesis and secretion in the pancreas, resulting in insulin resistance in peripheral tissues and eventually causing hyperglycemia, also known as diabetes (17,18). Steroids are one of the most important weapons used for inflammation caused by the virus in the COVID-19 infection. The fact that high amounts of pro-inflammatory cytokines were detected in the serum and respiratory samples of patients showed that immune modulation, i.e., suppression of the immune system, is important in the fight against disease. In fact, the use of immunosuppressive drugs like steroids has made significant contributions to reducing COVID-related morbidity and mortality (19). Therefore, steroids, which are widely used all over the world during COVID-19, have also been widely used in our country and in our hospital. Almost all of our patients have taken pulse steroids. As a result, the number of patients with dysglycemia at the time of discharge was determined to be higher than that at the beginning. This may be due to steroid use, and it may have developed due to β-cell damage and cytokine storms caused by the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) virus in the pancreas. In addition, the fact that the immune system is already impaired in uncontrolled diabetes has led to diabetic patients being more affected by SARS-CoV-2 and more hospitalizations (20). Given this information, it was thought that COVID-19 infection and steroid usage are important risk factors for DM and preDM development, and DM and preDM further increase the need for ICU, but there is no relationship between DM and FGF-21. However, the small number of patients may have limited the detection of a significant relationship.

Examining the results, it can be seen that there was a significant increase in the creatinine level and a significant decrease in lymphocytes and CRP. These findings are expected in hospitalized COVID-19 patients (21). There was no relationship between the FGF-21 level and gender. There is no evidence of this in the literature, either.

Ajaz et al. (9) investigated mitochondrial functions in healthy individuals, COVID-19-infected patients, and patients with pulmonary infection. They examined the FGF-21 and IL-6 levels in these participants. They have shown an increase in the utilization of glucose and glycolysis in COVID-19-infected patients. It was determined that there was a correlation between the severity of the COVID-19 infection and the increase in FGF-21 and IL-6 levels. Furthermore, it was reported that the HbA1c level was remarkably high in the COVID-19-infected group. However, no relationship was found between FGF-21 and glucose metabolism in this study, which may be because of the limited number of patients. Mitochondrial functions are the main factor in the natural immune response to viral infections (22).

Yan et al. (23) studied 193 patients with severe COVID-19 infection and found that the clinical course

was worse and mortality was higher in those with DM. Similarly, it was determined in this study that patients hospitalized in the ICU had more DM and preDM than patients hospitalized in the general ward.

In some previous studies, it was shown that FGF-21 cytokine levels increased in both diabetic patients and individuals with other metabolic diseases (24,25). Level is observed to increase in cases of insulin resistance, DM, and obesity. In the study, the increasing level of FGF-21 at the moment of discharge indicates that the action of this molecule promotes the functioning of the immune system and its fight against COVID-19.

Study Limitations

The presented study has some limitations. The small number of patients is the most important limitation, which restricts more specific results. Because the patients were hospitalized, their general condition was critical. Therefore, almost all of them had to be administered steroids. This may have affected the results achieved regarding glucose metabolism. Despite the limitations mentioned above, this study shows that there is a new parameter that can be used when fighting COVID infection, which is FGF-21. Fibroblast growth factor-21 is more specific than markers used in infection monitoring, such as CRP. Therefore, it is easy to track the COVID infection.

Conclusion

Fibroblast growth factor-21 metabolism is closely related to COVID-19 infection. It is activated in the fight against COVID-19. It can play an effective role in the healing process. The increase in FGF-21 can be used as a parameter to indicate that the COVID infection is healing.

Ethics

Ethics Committee Approval: The ethical approval was obtained from the Tokat Gaziosmanpasa University Faculty of Medicine, Clinical Research Ethics Committee (approval no.: 21-KAEK-165, date: 01.07.2021).

Informed Consent: Informed consent was taken from all the participants.

Authorship Contributions

Concept: A.D.D., Z.Ç., F.M.Z., Design: A.D.D., Z.Ç., F.M.Z., Data Collection or Processing: A.D.D., Z.Ç., F.M.Z., Analysis or Interpretation: A.D.D., Z.Ç., F.M.Z., Literature Search: A.D.D., Z.Ç., F.M.Z., Writing: A.D.D., Z.Ç., F.M.Z.

Conflict of Interest: No conflicts of interest were declared by the authors.

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