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DİSLİPİDEMİ VE COVİD 19 ENFEKSİYON RİSKİ ARASINDAKİ İLİŞKİ

THE RELATIONSHIP BETWEEN DYSLIPIDEMIA AND THE RISK OF COVID 19 INFECTION

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ÖZET

AMAÇ: Son zamanlarda ortaya çıkan koronavirüs (COVID-19) salgını, küresel bir halk sağlığı sorunu haline gelmiştir. Hipertansiyon, diabetes mellitus, obezite, kronik kalp ve akciğer hastalıkları, COVID-19 enfeksiyonu ve ciddi COVID-19 hastalığı gelişme riskini artırır. Bu çalışmada; hiperlipideminin tek başına COVID-19 enfeksiyonu gelişme riskini artırıp artırmadığını amaçladık.

GEREÇ VE YÖNTEM: Bu çalışmaya COVID-19 tanısı ile hastaneye yatırılan ve herhangi bir kronik hastalığı olmayan 134 hasta ile 122 sağlıklı kontrol alındı. Hasta grubunun başvurudan önceki son 6 aydaki lipid değerlerinin ortalaması hesaplandı. Kontrol grubunun da yine son 6 aylık lipid parametrelerinin ortalaması alındı.

BULGULAR: İki grup arasında yaş, cinsiyet ve laboratuvar özellikleri açısından fark yoktu. COVID-19 hastaları, kontrol deneklerine kıyasla önemli ölçüde daha yüksek trigliserit ve düşük yoğunluklu lipoprotein kolesterol değerlerine ve önemli ölçüde düşük yüksek yoğunluklu lipoprotein kolesterol seviyelerine sahipti ($p < 0.01$).

SONUÇ: Dislipidemi ve COVID-19 ile ilgili mevcut araştırmalar sınırlı olmakla birlikte, bulgularımız serum kolesterol düzeylerinin COVID-19 gelişme riski ile önemli ölçüde ilişkili olduğunu göstermektedir.

ANAHTAR KELİMELER: Covid-19 Virüs, Dislipidemi, Risk faktörleri

ABSTRACT

OBJECTIVE: The recent coronavirus disease 2019 (COVID-19) outbreak has become a worldwide public health problem. Hypertension, diabetes mellitus, obesity, chronic heart and lung diseases increase the risk of development of COVID-19 infection and severe COVID-19 disease. In this study; we aimed to investigate whether hyperlipidemia alone increases the risk of development of COVID-19 infection.

MATERIAL AND METHODS: One hundred-thirty four patients who were hospitalized with the diagnosis of COVID-19 and did not have any chronic disease and one hundred-twenty-two healthy controls were included in this study. The average of the lipid values of the patient group in the last 6 months before admission was calculated. Likewise, the average of the lipid parameters of the control group in the last 6 months was taken.

RESULTS: There were no differences between two groups with regard to age, gender, and laboratory characteristics. Triglyceride and Low-density lipoprotein cholesterol values were significantly higher and High-density lipoprotein cholesterol levels were significantly lower in the COVID-19 patients compared to the control subjects ($p < 0.01$).

CONCLUSIONS: Although research on the association of dyslipidemia with COVID-19 is still insufficient, our findings show that serum cholesterol levels are significantly associated with the risk of COVID-19 infection.

KEYWORDS: Covid-19 Virus, Dyslipidemia, Risk factors

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INTRODUCTION

Coronavirus Disease 2019 (COVID-19) was reported for the first time in December 2019 in Wuhan, China, as the severe acute respiratory distress syndrome caused by the The SARS-CoV-2 (1, 2). The SARS-CoV-2 infection outbreak has been named by the World Health Organization (WHO) as COVID-19 (2). The virus spread very quickly around the world and according to the data of the WHO, 242 million cases and 4.91 million deaths were reached as of 20.10.2021.

This disease is transmitted from person to person, especially adults are susceptible to COVID-19, and the severity of the disease has been shown to be related to age and chronic diseases of the patient. It has been shown that the disease progression is more seriously in people with comorbidities such as hypertension (HT), diabetes mellitus (DM), cardiovascular disease. In a meta-analysis, it was found that 17% of patients have coexisting HT, 8% DM, 5% cardiovascular diseases in and 2% respiratory system disease (3, 4).

Even in the early stages of the disease, there is evidence of arterial and venous coagulopathy in 8-15% of patients (5). Thrombosis of deep veins may lead to pulmonary embolism and thrombosis of the arterial system may lead to stroke and myocardial infarction in these patients. Thus, coagulopathy is the major contributing factor of mortality in COVID-19. Studies demostrate that activation of coagulation cascade and endothelial dysfunction is an independent factor on the severity and mortality of the disease (5).

Mortality in COVID-19 patients without comorbidity is 0.9%, but the ratio increases as the comorbidities being added. Mortality reaches 10.5% with coexisting cardiovascular diseases, 7.3% with DM and 6% with HT (6). This may be attributed to the effect of the hyperinflammatory response combined with endothelial dysfunction.

Hyperlipidemia is one of the major risk factors of cardiovascular diseases and is a co-factor for HT, obesity, DM progression. Dyslipidemia causes vascular endothelial dysfunction and begets many of the metabolic and vascular complications of these diseases.

Total cholesterol (TC) and Low-density lipoprotein cholesterol (LDL-c) levels have been reported to decrease in patients during the COVID-19 infection process (7); This decrease in LDL-c and Trigliserid (TG) levels in COVID-19 patients with dyslipidemia is related to the severity of the disease. This finding suggests a pathophysiological interaction between lipid metabolism and vessel damage (7, 8). High-density lipoprotein cholesterol (HDL –c) level decreases significantly only in critical cases (8). Therefore, LDL is the thought to be major factor contributing to the dyslipidemia in COVID-19 infection.

Dyslipidemia that occurs during COVID-19 infection is thought to be caused by many complex biological processes triggered by SARS-CoV-2. SARS-CoV-2reduces the uptake and biosynthesis of LDL-c by disrupting liver functions. Besides that, there is a moderate increase in aspartat aminotransferase (AST), alanin aminotransferase (ALT), and alkaline phosphatase (ALP) levels, which are markers of hepatic functions, in less than half of the patients (7, 8).

Both viral infection of endothelial cell (EC) and endothelial dysfunction at atherosclerotic areas may trigger thrombotic events at vascular bed. It has been concluded that cholesterol is required for early replication of SARS virus in host cells (9). Therefore, cholesterol participates in SARS-CoV-2 replication in host cells, including ECs. One of the hypothesis is that, the infected EC triggers coagulopathy and also local and acute damage of the blood vessels. The other hypothesis is that, the accumulation of oxidative LDL-c in the subendothelium forms an early step of atherogenesis (10). Unstable atherosclerotic plaques that are enriched by inflammatory cells and lipids, release high thrombogenic contents and trigger the onset of thrombotic occlusion. The death rate of COVID-19 infection in patients with cardiovascular disease reaches 10.8% and heart involvement especially in the form of acute myocardial injury is the major manifestation.

MATERIAL AND METHOD

The study was performed in Bursa High Specialized Education Research Hospital. It was planned as an obsevational case-control study. 134 patients who were hospitalized with COVID-19

diagnosis and positive nasopharyngeal swab PCR test between April 15 and June 15 2020, were enrolled in the study.

Since hypolipidemia developed during the COVID 19 infection process, the lipid values of these patients in the last 6 months before hospitalization were examined. 122 healthy adults were included in the control group. In the control group, all routine biochemical values, including lipid parameters in the last 6 months, were checked (such as glucose ,ürea, creatinine, hematocrit, hemogram). The lipid parameters measures in the last 6 months were also evaluated and averaged.

The exclusion criteria in our study were: Hypertension, diabetes mellitus, dyslipidemia treatment, coronary artery disease (chronic or acute coronary syndromes), cerebrovascular diseases, peripheral artery disease, known malignancy, heart failure (left ventricular ejection fraction; LVEF 45% or diastolic heart disease), liver dysfunction, renal failure (serum creatinine 110 µmol / L in men and 90 µmol / L in women), thyroid dysfunction and moderate or severe valvular disease.

Ethical Committee

The study was approved by the Bursa High Education Research Hospital Ethics Committee (Approval ID: 2020/148 date: 11.04.2020) and was conducted in accordance with the Helsinki declaration. Written informed consent was obtained from all patients.

Statistical Analysis

All statistical calculations were made by using SPSS statistics software (SPSS for Windows 25.0, Inc., Chicago, IL, USA). Continuous variables are given as mean ± SD, categorical variables are shown as percentages. The normal distribution of continuous variables was tested using the Kolmogorov-Smirnov test. To compare one group with another for continuous variables, Student's t-test was used. Categorical variables were compared by using the x^2 -test. All tests of significance were two-tailed. Statistical significance was defined as $p< 0.05$.

RESULTS

Of the 134 patients in the study group, 70 were male, 64 were female, and the mean age was 39.6 years. There were 63 males and 59 females in the control group and the mean age was 37.9 years. There was no significant difference between the groups in terms of age and gender parameters. The groups had similar characteristics in terms of basic biochemical and haematological values (hemoglobin, hematocrit, white blood cell count, glucose, creatinine, uric acid) in blood tests.

TG and LDL-c levels were higher and HDL-c level was lower in the COVID-19 group compared to the control group (TG: 267 ± 101mg/dl and 159 ± 56 mg/dl, $p < 0.001$, LDL-c: 145 ± 30 mg/dl and 100 ± 24 mg/dl, $p < 0.001$, HDL-c: 36 ± 7 mg/dl and 42 ± 12 mg/dl, $p = 0.008$, respectively). The difference between the groups was statistically significant **(Table 1)**.

Table 1: Clinical characteristics of COVID-19 patients and control subjects

Variable (mean)	Covid 19 group (n=134)	Control group (n=122)	P value
Age(year)	39.6 ±5.7	37.9±5.1	0,812
Gender (male/female)	26/24	23/27	0,517
Height(cm)	168±9	171±8	0,231
Weight(kg)	79±10	81±9	0,345
BMI	28	28	0,857
White Blood Cell count (10^3/ml)	7,1±2,5	6,8±1,9	0,741
Hemoglobin(g/dl)	13,5±1,8	13,2±1,8	0,287
Hematocrit (%)	40,4±4,7	38,8±5,5	0,593
Glucose (mg/dl)	98±12	94±10	0,421
Creatinine (mg/dl)	0,95±0,6	0,76±0,18	0,156
Uric acide (mg/dl)	5,6±1,9	4,9±1,3	0,124
Trigliserid (mg/dl)	267±101	159±56	<0,001*
LDL-c (mg/dl)	145±30	100±24	<0,001*
HDL-c (mg/dl)	36±7	42±12	0,008*

The covid 19 group and the control group are similar in basic characteristics. However, in the covid 19 group, TG and LDL-c were significantly higher and HDL-c was again significantly lower.
(LDL-c: Low-density lipoprotein cholesterol, HDL-c: High-density lipoprotein cholesterol BMI: Body Mass Index)
*: shows statistically significant values. (p<0.05)

DISCUSSION

There are two possible mechanisms underlying the relationship between dyslipidemia and COVID-19 infection. Firstly, hyperlipidemia may increase coagulopathy in COVID-19 patients and thus results in endothelial dysfunction (11, 12). In addition, cholesterol is required for the virus replication in the host cell (13). In the second manner, liver dysfunction arising in the course of COVID-19 infection may cause hyperlipidemia too. Behind these aspects, there is an interesting relationship between hypolipidemia and severity, prognosis of the disease (14).

Comorbid conditions like hypertension, diabetes mellitus, chronic kidney disease, chronic lung disease, cardiovascular disease, cancer, obesity may lie behind the suscepitibility of some patients to COVID-19 infection. These comorbidities also increases the risk of mortality and disease progression of COVID-19. As hyperlipidemia is also a predisposing factor for all these diseases, it may increase susceptibility to COVID 19 infection. Wei et al. found out that the major comorbidities in patients with COVID-19

in Wuhan are HT (32%), DM (12%) and cardiovascular disorders (8%) (15). Another study with 388 patients from Italy displayed 47.2% prevalence for HT, 22.7% prevalence for DM, 13.9% prevalence for coronary artery disease. In a meta-analysis of six studies conducted in China (including a total of 1527 patients); It has been shown that the prevalence of HT in COVID-19 patients is 17.1%, the prevalence of cardiovascular/cerebrovascular disorders is 16.4%, and the prevalence of DM is 9.7% (16).

The mortality risk of COVID-19 infection is quite high in patients with cardiovascular disease (10.8%) and manifestation of heart involvement especially seen as acute myocardial damage (17). Statins are known to have mortality and morbidity reducing effect on acute coronary events and may be expected to decrease cardiovascular complications in COVID-19 patients. Therefore, it seems reasonable to continue statin treatment in COVID-19 (18). There are studies disclosing that response to the treatment is better in patients with pneumonia receiving statin therapy than non-receivers. In a study by Grudzinska et al. (18) it has been demonstrated that statin treatment reduced in-hospital mortality in patients with community-acquired pneumonia. Surprisingly these patients were older, had diabetes more frequently and longer hospital stay than the control group. Although the mechanism is not fully elucidated, the anti-inflammatory and pleiotropic effects of statins is thought to play a role.

Statins have immunomodulating and anti-inflammatory effects via controlling excessive cytokine release in the immune system in influenza infection and thus preventing the intense inflammatory response (19, 20).

It is known that hyperlipidemia has an inflammatory effect and causes endothelial damage. Endothelial damage may increase the risk of contracting COVID-19 infection. It can be considered as a stand-alone risk factor for COVID-19 infection, as it both paves the way for comorbid diseases and causes endothelial damage. In our study, healty individuals with the same characteristics were compared with the group without a chronic disease who contracted COVID-19 infection. Lipid parameters were significantly higher in those with COVID-19 infection. This suggests that hyperlipidemia may be a risk factor for COVID-19 infection.

In this study, patients with HT, DM and heart disease were excluded. Our aim was to investigate whether the hyperlipidemia is a risk factor for COVID-19 infection risk or not. According to the results, even in the absence of diseases that result in endothelial dysfunction, hyperlipidemia alone increases the risk of COVID-19 infection.

There is a complex relationship between COVID-19 infection and lipid metabolism. In the course of COVID-19 infection, hypolipidemia develops, the degree of hypolipidemia is closely related to the severity of symptoms and mortality. On the other hand, hyperlipidemia eases endothelial dysfunction, increases coagulopathy and results in increased COVID-19 infection risk and poor prognosis. It is therefore a risk factor for COVID-19 infection and need to be controlled to prevent the spread of the COVID-19.

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