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Investigation of the Relationship Between COVID-19 Severity and Serum Adropin Levels

COVID-19 Şiddeti ile Serum Adropin Düzeyleri Arasındaki İlişkinin Araştırılması

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ABSTRACT

Objective: COVID-19 is a multisystemic disease with high mortality and morbidity. It is very important to understand the pathogenesis of the disease and to develop pharmacological treatment methods. The aim of this study was to measure serum adropin levels in COVID-19 patients in the ward and intensive care unit and to investigate whether this value can be a prognostic factor or a pharmacological treatment target.

Methods: 116 volunteer participants were included in the study. Participants were grouped as the control group consisting of patients without any disease, patients diagnosed with COVID-19 and hospitalised in the ward, patients diagnosed with COVID-19 and hospitalised in Level 2 intensive care and patients diagnosed with COVID-19 and hospitalised in Level 3 intensive care. Venous blood was taken from the patients. Serum adropin levels were measured according to the manufacturer's instructions. ROC analysis was also performed.

Results: According to serum adropin measurements, serum adropin levels of patients with COVID-19 who were hospitalised in the ward decreased compared to the control group. In Level 2 intensive care and Level 3 intensive care patients, serum adropin levels decreased compared to patients in the ward. According to Roc analysis, 333.1 ng/L adropin had a specificity of 0.8167 (95%, 0.6956-0.9048) and a sensitivity of 0.6522 (95%, 0.4273-0.8362).

Conclusion: COVID-19 is a disease with high mortality and morbidity affecting all systems. With this study, we think that serum adropin levels may be a prognostic factor or a new pharmacological treatment target and may shed light on new studies.

Keywords: COVID-19, SARS CoV-2, Endothel, Adropin

ÖZ

Amaç: COVID-19 hastalığı mortalitesi ve morbiditesi oldukça yüksek olan multisistemik bir hastalıktır. Hastalığın patogenezini anlamak ve farmakolojik tedavi yöntemleri geliştirmek oldukça önemlidir. Bu çalışmanın amacı COVID-19 hastalarında serviste ve yoğun bakımda yatan hastaların serum adropin seviyelerini ölçmek ve bu değerin prognostik bir faktör ya da farmakolojik bir tedavi hedefi olup olamayacağını araştırmaktır.

Yöntemler: 116 gönüllü katılımcı araştırmaya dahil edilmiştir. Katılımcılar herhangi bir hastalığı olmayanlardan oluşan kontrol grubu, COVID-19 tanısı alıp serviste yatan hastalar, COVID-19 tanılı 2. Düzey yoğun bakımda yatan hastalar ve COVID-19 tanılı 3. Düzey yoğun bakımda yatan hastalar olmak üzere gruplandırılmışlardır. Hastalardan venöz kan alınmıştır. Serum adropin düzeyleri üretici firmanın direktifleri doğrultusunda ölçülmüştür. Ayrıca ROC analizi yapılmıştır.

Bulgular: Yapılan serum adropin ölçümlerine göre serviste yatan COVID-19 tanılı hastaların serum adropin düzeyleri kontrol grubuna kıyasla düşmüştür. 2. Düzey yoğun bakım ve 3. Düzey yoğun bakım hastalarında ise serviste yatan hastalara kıyasla serum adropin seviyeleri düşmüştür. Yapılan Roc analizine göre de 333.1 ng/L adropinin 0.8167(95%, 0.6956-0.9048) ve 0.6522(95%, 0.4273-0.8362) spesifitesi mevcuttur.

Sonuç: COVID-19 tüm sistemleri etkileyen mortalitesi ve morbiditesi yüksek olan bir hastalıktır. Bu çalışmamızla serum adropin düzeylerinin prognostik bir faktör ya da yeni bir farmakolojik tedavi hedefi olabileceğini ve yeni çalışmalara ışık tutabileceğini düşünüyoruz.

Anahtar Kelimeler: COVID-19, SARS CoV-2, Adropin, Endotel

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Introduction

Coronavirus Disease 2019 (COVID-19) is a disease with multisystemic involvement caused by the highly contagious severe respiratory coronavirus syndrome coronavirus 2 (SARS CoV-2) (Hu et al., 2021). Most patients have a mild illness with symptoms such as sore throat, fever, mild cough and loss of taste and smell. In hospitalised patients, conditions with higher morbidity and mortality such as

COVID-19 pneumonia, acute respiratory distress syndrome (ARDS), multiorgan failure may develop (Elrobaa & New, 2021). The prognosis was worse in patients with advanced age (>75 years), arterial hypertension, diabetes mellitus (DM), pre-existing cardiac or respiratory disease and obesity. Other poor prognostic laboratory parameters are O2 saturation below 88, lymphopenia, thrombocytopenia, increased LDH, CRP >200 mg/dl, D-Dimer >2500 ng/ml, increased troponin and ferritin >2500 ng/ml at the time of admission (Long et al., 2022). However, none of these are significant on their own and more specific parameters are needed.

Adropin is a peptide that regulates glycolipid metabolism, found mainly in the brain and liver, but also in the heart, gastrointestinal tract and circulatory system (Aydın et al., 2022). Encoded by the energy homeostasis associated gene (Enho) (Jasaszwili et al., 2020). Adropin levels have been studied in patients with DM, a pathology accompanied by endothelial dysfunction due to its effects regulating lipid and carbohydrate metabolism. Serum adropin levels were significantly lower in patients with DM (Ali et al., 2022). The relationship between adropin levels and diseases is not limited to these. Serum adropin levels were lower in patients with atrial fibrillation compared to healthy controls (Wang et al., 2019). In another study by Aydın et al. serum adropin levels were found to be significantly lower in COVID-19 disease (Aydın et al., 2022). In the evaluation of previous studies, it was thought that adropin is a parameter that can be used in differential diagnosis and shaping treatment protocols in diseases accompanied by endothelial dysfunction such as COVID-19.

In this study, we examined whether adropin, which was found to be lower in COVID-19 disease, could be a prognostic factor in COVID-19 disease. Thus, we also investigated the feasibility of adropin and related mechanisms as new therapeutic targets in conditions accompanied by viral and endothelial damage such as COVID-19.

Methods

Study Design

A total of 116 participants, including 89 patients diagnosed with COVID-19 and hospitalised in Erzurum Regional Training and Research Hospital and 27 healthy volunteers, were included in the study. Participants and/or 1st degree relatives of the participants were informed about the study. It was explained that blood samples would be taken. Voluntary consent forms were obtained. Participants were grouped as follows:

Control Group: 27

Inpatients in the ward: 29

Level 2 Intensive Care Unit Inpatients: 37

Level 3 Intensive Care Unit Inpatients: 23

COVID-19 RT PCR test was performed in all participants. Patients with goitre, coronary artery disease, atrial fibrillation, congestive heart failure, hypertension, chronic renal failure and cancer were not included in the study.

Sample Collection

Blood samples obtained from the volunteers participating in the study were collected in tubes containing non-ethylenediamine tetra acetic acid. The collected blood samples were centrifuged at 4000 rpm for 10 minutes at +4 °C. Serum samples were separated from the tubes and stored at -80 °C until the time of use.

Measurement of Serum Adropin Levels

Serum Adropin Levels were measured according to the manufacturer's instructions (Bioassay Technology Labarotory, Wuhan, China). The reference range is 5- 10 000 ng/L.

Statistical Analysis

GraphPad Prism5 version was used to evaluate statistical differences among groups. One Way ANOVA followed by Tukey HSD was used to compare parametric values. ROC curve analysis was used to test whether adropin value is a significant marker in COVİD infection. $p<0.05$ was considered statistically significant.

Results

Characteristics of Hospitalized Patients

Of the patients included in the study, 29 were hospitalised in the ward, 27 in Level 2 intensive care unit and 23 in Level 3 intensive care unit. Of these patients, 64% were female and 36% were male. Tomography uptake compatible with severe COVID-19 was present in 44% and moderate in 56% of the patients. Other characteristics of the groups are summarised in Table 1.

Adropin Levels in Patients and Healthy Individuals

We measured adropin levels in patients and healthy individuals as shown in Figure 1. The results showed that healthy individuals had higher levels of adropin than patients ($p<0.05$). In addition, adropin levels were significantly different in patients treated in the ward, second-level intensive care unit, and third-level intensive care unit ($p<0.05$). It was observed that the serum adropin level decreased inversely with the care level needs of the patients.

ROC Curve Analysis of Adropin

The discriminative power of adropin was evaluated via ROC curve analysis that is presented in Figure2. The area under the curve (AUC) of adropin was 0.853 (p<0.0001). At the cut of value of 333.31 ng/L adropin had 0.8167 (95%, 0.6956-0.9048) sensitivity and 0.6522 (95%, 0.4273-0.8362) specificity to discriminate patients with COVID-19 infection from healthy individuals.

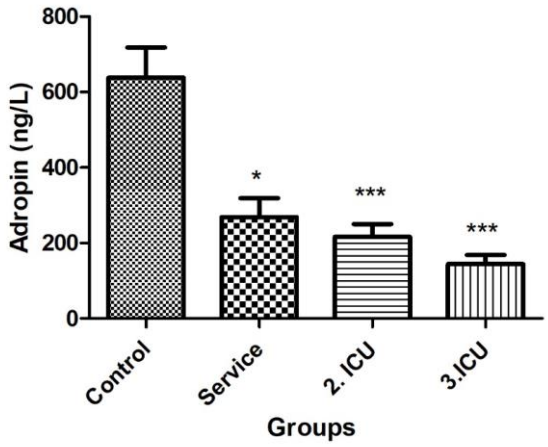

Figure 1: Serum adropin levels in healthy individuals and patients needing different levels of care.

ICV: Intensive Care Unit, * means p<0.05, *** means p<0.001 according to control group. Results were analyzed with one-way ANOVA-Tukey test.

Discussion

In this study, we compared the serum adropin levels of patients in the control group, patients hospitalised in the ward with a diagnosis of COVID-19 and patients hospitalised in intensive care with a diagnosis of COVID-19 and showed that there was a statistically significant difference. Serum adropin levels were found to be lower in patients hospitalised in the ward compared to the control group. In patients hospitalised in 2nd and 3rd level intensive care unit, it was found to be lower than both the patients hospitalised in the ward and the control group. However, no significant difference was observed between the serum Adropin levels of patients hospitalised in Level 2 intensive care unit and patients hospitalised in Level 3 intensive care unit. We also measured the sensitivity and specificity of serum Adropin levels for COVID-19 patients in the Roc analysis. In the light of all these evaluations, we thought that serum Adropin levels could be used as a prognostic factor in COVID-19 disease. In addition to its contribution to diagnosis, we have shown that adropin levels can be a target parameter both in the selection of treatment and in the development of new pharmacological treatments in the future.

COVID-19 disease causes a lung-centred injury affecting the vascular endothelium (Bonaventura et al., 2021). SARS-CoV-2 can directly infect endothelial cells and cause cellular damage (Teuwen et al., 2020). SARS-CoV-2 virus enters the cell via ACE2 transmembrane protein. ACE2 receptors are expressed in the lung, heart, kidneys, small intestine and endothelium (Ferrario et al., 2005). SARS-CoV-2 viral particles were observed in lung and kidney endothelial cells. Infection-mediated endothelial damage and endothelitis have been observed in many vascular beds such as lung, heart and kidney (Varga et al., 2020).

Endothelial cells are vitally important for the maintenance of vascular homeostasis. While healthy endothelium expresses various factors to ensure vascular relaxation and blood flow, it also inhibits platelet aggregation and coagulation. However, when endothelial dysfunction develops, this balance shifts in favour of coagulation (Yau et al., 2015). This is also seen in COVID-19 infection as endothelial damage develops. Endocan levels, a protein expressed in the endothelium, were found to be higher in COVID-19 patients compared to the healthy control group (Laloglu & Alay, 2022). Autopsies performed in patients with COVID-19 showed disruption of the endothelial cell membrane and thrombosis with occlusion and microangiopathy in alvolar capillaries (Ackermann et al., 2020). It is known that pulmonary microthrombi developing due to endothelial dysfunction also contribute to the development of ARDS, which is a vital complication due to COVID-

Table1: Characteristics of Inpatients

Number of Inpatients by Service	
Service	29
Level 2 Intensive Care Unit	37
Level 3 Intensive Care Unit	23
Age Median (Min, Max) Years	
Service	70 (23-87)
Level 2 Intensive Care Unit	76 (46-95)
Level 3 Intensive Care Unit	69 (39-86)
Median SpO2 values (Min, Max)	
Service	89 (75-94)
Level 2 Intensive Care Unit	85 (70-93)
Level 3 Intensive Care Unit	80 (65-85)
Median Number (Min, Max) of Hospitalization Days	
Service	14 (6-50)
Level 2 Intensive Care Unit	25 (4-70)
Level 3 Intensive Care Unit	28 (2-90)

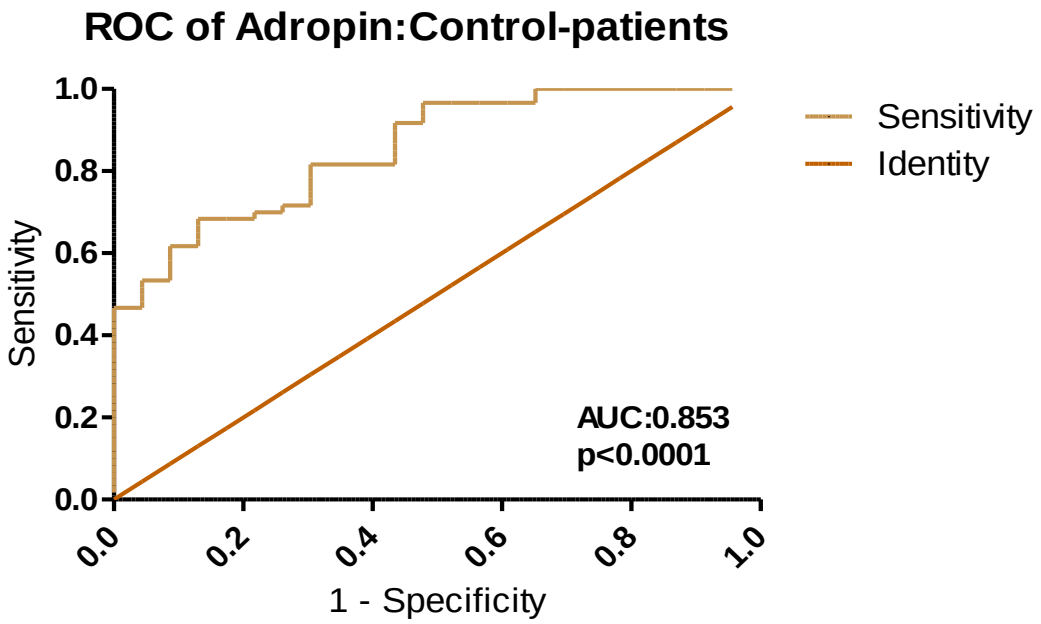

Figure 2: ROC Curve Analysis of Adropin to discriminate patients from healthy individuals

19. Again, Goshua et al. reported that endotheliopathy due to COVID-19 may be associated with critical illness and death.

Adropin is a hormone involved in the maintenance of energy homoeostasis and insulin response, identified in 2008 by Kumar et al. (Kumar et al., 2008). Adropin stimulates insulin release via AKT pathway (Gao et al., 2015). Adropin also has effects on lipid metabolism. The effects of adropin on adipogenesis were investigated in 3T3-L1 cell line and rat preadipocytes. In the study, adropin stimulated these cells and decreased lipid accumulation and proadipogenic gene expression (Jasaszwili et al., 2019). In another study, it was observed that serum triglyceride, total cholesterol and LDL-C levels decreased after adropin treatment applied to hyperlipidaemic rats (Akcılar et al., 2016). However, apart from these, adropin has important effects on endothelial functions. eNOS-derived NO is a potent vasodilator and inhibits platelet aggregation and adhesion (Förstermann & Sessa, 2012). Adropin increases eNOS expression via VEGF-PI3K-Akt and VEGFR2-ERK1/2 pathways and protects the endothelium (Lovren et al., 2010). Coronary artery disease is a clinical condition with high mortality and morbidity. Endothelial dysfunction, lipid metabolism disorders and vascular inflammation play an important role in the pathogenesis of coronary artery disease. In a meta-analysis of 525 patients with coronary artery disease and 420 healthy controls, serum adropin levels were found to be lower in patients with coronary artery disease compared to healthy controls (Zheng et al., 2019). The study by Sato et al. demonstrated the effect of adropin on atherosclerosis molecularly. Adropin was shown to attenuate the inflammatory response of endothelial cells and monocyte derived macrophages. It also reduced migration and proliferation of vascular smooth muscle cells (Sato et al., 2018). In another study, adropin decreased endothelial permeability in rat brain ischaemia by inhibition of the ROCK-MLC2 pathway (Yang et al., 2016). The relationship between DM and serum adropin was also analysed. In the study by Wu et al. serum adropin levels were found to be significantly lower than in non-diabetic patients (Wu et al., 2014). In patients with diabetic retinopathy, a complication of diabetes, adropin concentrations in serum and vitreous fluid have been found to be negatively correlated with type 2 DM and diabetic retinopathy (Li et al., 2019). In another study, serum adropin levels were found to be higher in type 2 DM patients (Hosseini et al., 2016). However, in a meta-analysis of 15 studies with a total of 2813 participants, serum adropin levels in patients with type 2 DM were found to be lower than in patients without diabetes (Soltani et al., 2023). Diseases such as coronary artery disease, type 2 DM and obesity are clinical conditions in which both endothelial dysfunction and inflammation are observed. COVID-19 disease caused by SARS-CoV-2 is a disease in which both dysregulated inflammation and endothelial damage are observed. Level 2 and Level 3 intensive care unit patients had a statistically significant decrease in serum adropin levels compared to ward patients. These results suggest that serum adropin level may be both a prognostic marker and a target point for future pharmacological treatment strategies in COVID- 19 patients. However, this study has some limitations. The fact that it was not performed in a larger patient group by increasing the number of patients is a limitation. It is not known whether serum

adropin levels decreased gradually or whether there was a sudden decrease. In addition, the correlation between serum adropin levels and parameters indicating endothelial dysfunction or inflammation could have not been analyzed.

Conclusion and Recommendations

COVID-19 disease is an important disease affecting billions of people and affecting national health systems. A better understanding of the pathogenesis of this disease will contribute to the development of pharmacological treatment methods. The fact that serum adropin levels vary according to the severity of the disease suggests that adropin may be a prognostic factor. Therefore, we think that our study may shed light on larger and more comprehensive studies.

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