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ARAŞTIRMA MAKALESİ / RESEARCH ARTICLE

Serum Elebela Levels in Pulmonary Embolism

Akut Pulmoner Embolide Serum Elebela Düzeyleri

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ÖZET

Amaç: Akut pulmoner emboli sık karşılaşılan ve yüksek mortaliteye sahip bir pulmoner vasküler hastalık olup tanısı için geliştirilmiş spesifik bir biyobelirteç henüz bulunmamaktadır. Çalışmamızda akut pulmoner emboli tanısı alan hastaların başvuru anındaki serum Elabela düzeylerini incelemeyi, oksidatif stres düzeyleri ile Elabela düzeylerinin ilişkisini ve Elabela'nın tanısal değerini araştırmayı amaçladık.

Gereçler ve Yöntem: Çalışmaya 41 akut pulmoner emboli hastası ve kontrol grubu için 37 sağlıklı birey dahil edildi. Tüm katılımcıların serumlarından Elabela, Total Antioksidan ve Oksidan Kapasite düzeyleri ölçülerek sonuçlar karşılaştırıldı.

Bulgular: Akut pulmoner emboli hastalarında kontrollere kıyasla Elabela düzeyleri anlamlı derecede düşük, total oksidan kapasite, total antioksidan kapasite ve oksidatif stres indeksi değerleri anlamlı derecede yüksekti. Elabela seviyeleri total oksidan kapasite ve oksidatif stres indeksi ile anlamlı korelasyon gösterdi. Elabela seviyeleri D-Dimer, Troponin I değerleri arasında korelasyon yoktu. Elabela için yapılan ROC eğrisi analizinde % 75,7 duyarlılık ve % 90,2 özgüllük ile akut pulmoner emboli tanısı için gerekli seviye 220,18 ng /L idi. Eğri altındaki alan 0,82 ve % 95 CI 0,72-0,94 idi (p<0,001).

Sonuç: Bu çalışmada akut pulmoner emboli hastalarında Elabela düzeylerinin azaldığını gösterdik. Ayrıca total oksidan kapasite ile serum Elabela seviyeleri arasında negatif bir korelasyon gözlemledik. Yapılan çalışmaların sonucunda Elabela-apelin/APJ sistemi ile trombosit agregasyonu ve aterotromboz arasındaki ilişki halen belirsizdir. Bu yolağın netleşmesiyle Elabela'nın insanlarda akut pulmoner emboli için tanısal biyobelirteç ve terapötik ajan olarak rolünü belirlenmesine imkan sağlanacaktır. Bunun için daha büyük ve daha kapsamlı çalışmalara ihtiyaç vardır. Klinik tanıya katkı sağlaması durumunda serum Elabela ölçümü hasta açısından daha kolay, daha hızlı ve daha az invaziv olabilir.

Anahtar Kelimeler: Pulmoner emboli, elabela, oksidatif stress

ABSTRACT

Objective: Acute pulmonary embolism is a common pulmonary vascular disease with high mortality, and there is no specific biomarker developed for its diagnosis yet. In our study, we aimed to examine the serum Elabela levels at the time of admission in patients diagnosed with acute pulmonary embolism and the relationship between oxidative stress and Elabela, and the diagnostic value of Elabela.

Materials and Method: Forty-one acute pulmonary embolism patients and thirty-seven healthy individuals for the control group were included in the study. Elabela, Total Antioxidant and Oxidant Capacity levels were measured from the serums of all participants and the results were compared.

Results: Elabela levels were significantly lower, total oxidant and antioxidant capacity and oxidative stress index values were significantly higher in acute pulmonary embolism patients compared to controls. Elabela levels showed a significant correlation with total oxidant capacity and oxidative stress index. There was no correlation between Elabela and D-Dimer and Troponin I values. In the ROC curve analysis for Elabela, the level required for the diagnosis was 220.18 ng /L with a sensitivity of 75.7% and a specificity of 90.2%. The area under the curve was 0.82 and 95% CI was 0.72-0.94 (p<0.001).

Conclusion: In this study, we showed that Elabela levels were reduced in patients with acute pulmonary embolism. We also observed a negative correlation between total oxidant capacity and serum Elabela levels. As a result of the studies, the relationship between the Elabela-apelin/APJ system and platelet aggregation and atherothrombosis is still unclear. The clarification of this pathway will allow the determination of the role of Elabela as a diagnostic biomarker and therapeutic agent for acute pulmonary embolism. For this, larger and more comprehensive studies are needed. Serum Elabela measurement may be easier, quicker and less invasive for the patient if it contributes to clinical diagnosis.

Keywords: Pulmonary embolism, elabela, oxidative stress

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INTRODUCTION

Acute pulmonary embolism (APE), together with deep vein thrombosis, is the clinical manifestation of venous thromboembolism (1). APE is the third most common acute cardiovascular condition (2) and its prevalence is increasing over time (3). Currently, APE diagnosis is primarily based on the combination of blood tests and imaging analyses. Although the D-dimer test, which has a high false-positive rate, is a good option to "exclude" APE, it is not good in terms of "diagnosis". Although computed tomography pulmonary angiography is reported as the 'gold standard', it is not suitable for regular clinical screening. Its use is limited in patients with renal failure and hypersensitivity to iodine-containing contrast agents (4-6). Therefore, other non-invasive, easy-to-detect and reliable biomarkers are still needed for the diagnosis of APE.

Apelin and Elabela are two peptide ligands for a class A G-protein coupled receptor called the apelin receptor (AR/APJ/APLNR). These ligands function by binding to this receptor, known as the apelinergic system (Apelin/APJ system). Binding of both endogenous peptides to APJ results in similar physiological effects (7,8). Elabela has been found to localize in adult endothelium, human stem cells, and kidneys (9). Several studies have also shown that Elabela is associated with vasodilation, myocardial contractility, and pulmonary arterial hypertension in animal models (10–12). Apelin and Elabela are known to have protective effects on the cardiovascular system. In human and animal models, Elabela administration has been shown to cause systemic vasodilation, resulting in a significant decrease in blood pressure (12,13). Elabela is thought to have this effect by blocking the renin-angiotensin-aldosterone system via the APJ receptor, which is 31% structurally similar to the angiotensin II type 1 receptor (10). Yavuz et al. have shown that Elabela levels are reduced in patients with total coronary occlusion and that there is a positive correlation between coronary collateral development and serum Elabela levels (14).

Studies have found that the Elabela-apelin/APJ system plays an important role in thrombosis-related diseases such as atherosclerosis, myocardial infarction, and cerebral infarction. However, there is no study investigating serum Elabela levels in APE patients with thrombosis as the pathological basis. Therefore, we aimed to investigate the difference between serum Elabela levels in healthy individuals and APE patients, whether Elabela can be a biomarker in the diagnosis of APE, and the relationship between serum Elabela levels and oxidative status.

MATERIALS AND METHOD

Patient Selection and Data Collection

This study was planned prospectively between July 2021 and January 2023. The study included 41 patients who were admitted to the chest diseases clinic of a tertiary referral hospital with the diagnosis of APE and 37 healthy individuals who met the exclusion criteria and did not have APE. The diagnosis of APE was confirmed by Computed tomography pulmonary angiography. In the study; congenital cardiomyopathy, severe heart valve disease, chronic liver disease, chronic kidney disease (GFR <60 ml/kg/min), thyroid dysfunction, atrial fibrillation, acute coronary syndrome, malignancy, active infection, autoimmune diseases, rheumatological diseases ≤18 and ≥ 85 years of age patients were accepted as exclusion criteria.

Acele et al. (15) found a difference in Elabela levels between patients with complete AV block and healthy individuals in a study they conducted on patients with complete AV block. In the power analysis conducted based on this study, the test power was 0.95 and the error was accepted as 0.05, and the sample size in terms of Elabela levels should include at least 8 patients for each group. The local ethics committee (Kahramanmaraş Sütçü İmam University Non-Interventional Clinical Research Ethics Committee, 03.02.2021/86) approved the study protocol implemented in accordance with the principles set out in the Declaration of Helsinki. All subjects signed written informed consent before starting the study.

Demographic data were recorded. Heart rate and systolic and diastolic blood pressure were measured. The remaining serums from the blood samples taken for routine tests from individuals in the control group and patients diagnosed with APE before starting the treatment were separated for the study. The separated serum samples were frozen at -80 °C until analysis. D-Dimer, one of the routine laboratory parameters; Cobas 8000 c702 (Roche Diagnostic, Germany) autoanalyzer and Troponin I was analyzed by Radiometer Aqt 90 (Bronshoj, Denmark).

Elabela Measurement

Elabela serum levels were determined using a commercial enzyme-linked immunosorbent assay (ELISA) kit (Catolog No: NE010733101, NEPENTHE) with an automatic ELISA reader (Thermo Scientific, FINLAND) and a computer program (ScanIt for Multiscan FC 2.5.1) in accordance with the manufacturer's instructions. Sensitivity: 3.47 pg/L and assay range: 7 ng/L – 1500 ng/L. Intra-assay %CV was <8%, Inter-assay %CV was <10%. Results were determined as ng/L.

TOS, TAS Measurement

Total oxidant capacity: TOS levels were determined spectrophotometrically using Rel Assay commercial kits (Rel Assay Kit Diagnostics, Turkey). H_2O_2 was used as calibrator. Results were expressed as mol H_2O_2 equivalent/L.

Total antioxidant capacity: TAS levels were measured spectrophotometrically using Rel Assay commercial kits (Rel Assay Kit Diagnostics, Turkey). Trolox, a water-soluble vitamin E analog, was used as a calibrator. Results were expressed as mmol Trolox equivalent/L. Oxidative stress index (OSI) was calculated by dividing total oxidant capacity (TOS) by total antioxidant capacity (TAS) (16).

Statistical Analysis

Statistical analyses were performed using SPSS vn 22 program (IBM SPSS for Windows version 22, IBM Corporation, Armonk, NY, USA). Kolmogorov-Smirnov test was used to assess the conformity of the data to normal distribution. Independent T test was used for groups with normal distribution and Mann-Whitney U test was used for groups with non-normal distribution. Independent Chi-Square Test was used for age

and gender comparisons of the groups. Correlations between variables were evaluated with Spearman Correlation test. Diagnostic decision-making properties of elabela levels in predicting the disease were analyzed with ROC curve analysis. Descriptive variables were expressed as median (minimum-maximum) and mean±standard deviation, categorical data as percentage. P<0.05 was used for statistical significance.

RESULTS

The demographic characteristics of the acute pulmonary embolism and control groups are given in Table 1. The patient group in the study consisted of an older population, with the mean age of the APE patient group being 59.17 and the mean age of the control group being 36.94. There was no significant difference between the groups in terms of gender. Elabela levels were significantly lower, and TOS, TAS and OSI values were significantly higher in APE patients compared to controls (p value <0.001; <0.001; 0.47; <0.001, respectively) (Table 2) (Figure 1).

Elabela levels showed significant correlation with TOS and OSI (r= -0.423, r= -0.414; p= <0.001, respectively). There was no correlation between serum Elabela levels and D-Dimer, Troponin I values in APE patients. (Table 3) Serum D-Dimer levels in APE patients were 10.6±12.42 and Troponin I levels

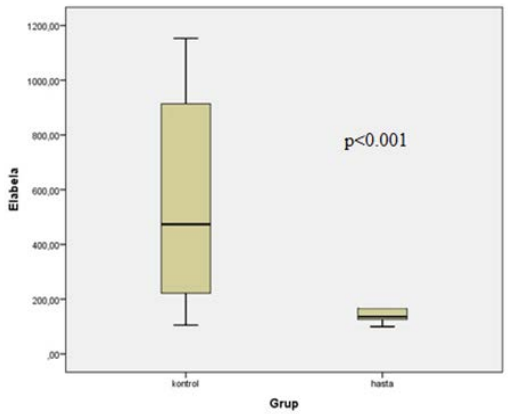

Figure 1. Levels of Correlation Between Study Groups Error bars indicate standard deviation.

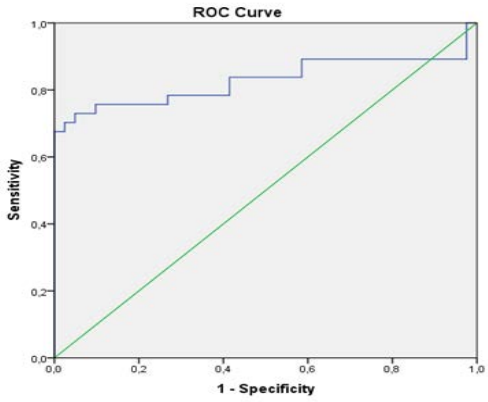

Figure 2. ROC Curve for Elabela in Acute Pulmonary Embolism (Area under the curve: 0.82)

Table 1. Demographic findings of the study population

	Patient Group (n= 41)	Control Group (n=37)	p Value
Gender (F/M)	14/27	11/26	0.676¥
Age (mean±standard deviation)	59.17±16.47	39.95±8,84	<0.001*α
Smoking (smoker/non-smoker)	11/30	16/21	0.128¥

*: indicates statistical significance ¥: Independent Chi-Square Test, α: Independent T Test

Table 2. Laboratory findings of the study population

	Patient (n= 41)	Control (n=37)	p Value
Elabela (ng/L) [median]	136.07 Q1=124.89 Q3=166.95	473.35 Q1=189.25 Q3=921.64	<0.001*β
TOS (μmol H_2O_2eq/L) [median]	41.45 Q1=14.56 Q3=65.55	5,91 Q1=3.02 Q3=8.94	<0.001*β
TAS (μmol Trolox eq/L) [median]	1.20 Q1=1.015 Q3=1.56	1.11 Q1=0.995 Q3=1.185	0.047*β
OSI (unitless) [median]	32.87 Q1=13.64 Q3=49.85	5,14 Q1=2.81 Q3=8.14	<0.001*β

TOS; Total Oxidant Status, TAS; Total Antioxidant Status, OSI; OSI; Oxidative Stress Index *: indicates statistical significance ¥: Independent Chi-Square Test, α: Independent T Test, β: Mann-Whitney U Test

Table 3. Correlation of plasma Elabela levels with clinical and laboratory parameters

Correlation	Correlation Coefficient (r Value)	Level
Elabela-TAS	-0.056	
Elabela-TOS	-0.423*	moderate
Elabela-OSI	-0.414*	moderate
Elabela-D-Dimer	-0.056	
Elabela-Troponin	0.098	
Elabela-CRP	0.099	
Elabela-Age	-0.449*	moderate
Elabela-SystolicTA	0.057	
Elabela-DiastolicTA	0.041	
Elabela-Pulse	0.042	

TOS; Total Oxidant Status, TAS; Total Antioxidant Status, OSI; OSI; Oxidative Stress Index *p <0.001 indicates statistical significance

were 0.28±0.42. In the ROC curve analysis for Elabela, the level required for APE diagnosis was 220.18 ng /L with 75.7% sensitivity and 90.2% specificity. The area under the curve was 0.82 and 95% CI was 0.72-0.94 (p<0.001) (Figure 2).

DISCUSSION

This study is the first to investigate serum Elabela levels in APE patients. The results of the study showed that serum Elabela levels were decreased in APE patients compared to healthy volunteers. In addition, TOS and OSI, which indicate total oxidative stress, were higher in APE patients and showed a negative correlation with serum Elabela levels.

In 1993, O'Dowd and colleagues identified a gene that they named APJ, which has an identity similar to the angiotensin II type 1 receptor (17). Later, in 1998, a new ligand, apelin, was discovered by Tatemoto and colleagues, which binds to this G protein-coupled receptor APJ (18). In the following years, other ligands such as Elabela and Tollder, which bind to APJ, were discovered and various physiological effects were investigated (19). Studies on the effects of apelin and Elabela on the cardiovascular system showed that they: i) contribute to the formation of the heart and angiogenesis during the embryogenic period; ii) have inotropic effects; iii) cause vasodilation in both the systemic and pulmonary vascular systems; iv) cause a decrease or slowing down of diseases that lead to cardiac hypertrophy and fibrosis; v) reduce peripheral vascular disease; and vi) they have shown to improve the clinical picture of heart failure and myocardial infarction (10). Therefore, it is thought that this could be a treatment method due to all these positive and cardiovascular protective effects (20).

Impaired endothelial function is associated with atherosclerosis. Elabela is mainly detected in fibroblasts and intact endothelial cells in the heart (21). Therefore, Elabela production decreases in impaired endothelial function. The low Elabela levels measured in the APE group in our study can be explained by the presence of impaired endothelial function. Yavuz et al. found low serum Elabela levels in chronic total occlusion patients with stable angina pectoris and associated them with impaired endothelial functions and impaired angiogenesis (14). In a study conducted in children with pulmonary stenosis, it was observed that serum Elabela levels were negatively correlated with the severity of pulmonary stenosis and that serum Elabela levels increased on the 3rd day after surgery in these children. In this study, it was stated that Elabela indicated right ventricular afterload (22). Human and mouse platelets express apelin and its receptor APJ. Apelin directly contributes to thrombin-mediated signaling pathways and platelet activation, secretion, and aggregation, but is ineffective against ADP- and thromboxane A2-mediated pathways. In an animal experiment, IV apelin given to rats was shown to cause excessive bleeding and prevent thrombosis. This study emphasized that apelin and/or APJ agonists may be potentially useful in antiplatelet therapies (23). Contrary to these data, some studies have shown that Elabela and other endogenous ligands such as apelin-12, -17, and -36 induce platelet aggregation and thrombosis (24). Again, some studies have detected high Elabela levels in MI patients with underlying thrombosis (25). In a study conducted in rats, apelin was shown to improve cardiac dysfunction after myocardial ischemic reperfusion injury by suppressing myocardial apoptosis and resisting oxidative effects through APJ receptor activation (26). A study reported that endogenous apelin in the pulmonary artery wall had no significant role in regulating pulmonary vascular tone in the acute phase of APE (27). In another study, no significant change was observed in the endogenous apelin level in the pulmonary artery wall in the early phase of APE, while an increase in apelin expression was observed in the bronchial epithelium (28). The levels of apelin 13, an adipokine that stimulates the APJ system like elabela, were examined in patients with pulmonary embolism, and higher apelin levels were detected in the patients compared to the healthy control group (29). In other words, there is no consensus on whether members of the APJ system such as elabela and apelin increase or decrease in either pulmonary embolism or other diseases. In the study conducted by Kavaklı et al., they found TOS and OSI values high in APE patients, but no significant difference was found in TAS values (30). The results of our study also supported this study. The negative correlation between TOS and serum Elabela levels indicates that Elabela levels decrease further with increasing oxidative load in patients, suggesting that this situation affects the pathogenesis of the disease.

In conclusion; in this study, we showed that Elabela levels are decreased in APE patients. We also observed a negative

correlation between total oxidant capacity and serum Elabela levels. As a result of the studies, the relationship between Elabela-apelin/APJ system and platelet aggregation and atherothrombosis is still unclear. Clarification of this pathway will allow the determination of the role of Elabela as a diagnostic biomarker and therapeutic agent for APE in humans. Larger and more comprehensive studies are needed for this. Serum Elabela measurement may be easier, faster and less invasive for the patient if it contributes to clinical diagnosis.

Limitations

This study has some limitations. First, the sample size was relatively small. The other is that since the ages of the individuals in the control and patient groups were different, it was not clear whether the measured parameters varied depending on age.

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