Elabela as a novel marker: Well-correlated with WIfI amputation risk score in lower extremity arterial disease patients

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Abstract

Objective: Worldwide, over 200 million people are diagnosed with lower extremity arterial disease (LEAD). LEAD significantly increases the risk of death and amputation of the lower limb. A new classification system (WIfI) has been proposed to initially assess all patients with ischemic rest pain or wounds and also predicts 1-year amputation risk. Elabela is a bioactive peptide and a part of the apelinergic system, which has beneficial effects on body fluid homeostasis and cardiovascular health. We aimed to investigate serum Elabela levels in LEAD.
Methods: A total of 119 subjects were enrolled in this cross-sectional study, 60 of whom were in the LEAD group and 59 in the control group. All participants underwent physical examination and routine biochemical tests, including serum Elabela levels. Additionally, the LEAD group was divided into subgroups according to the Rutherford classification, ankle-brachial index (ABI) values, and WIfI risk scores.
Results: Serum low-density lipoprotein, Elabela, and high-sensitivity C-reactive protein (Hs-CRP) levels were statistically higher in the LEAD group (p=0.002, p<0.001, and p<0.001, respectively). In the Rutherford classification, as the stage increased, Elabela and Hs-CRP levels increased similarly (p<0.001). Elabela levels were statistically found to be positively correlated with Hs-CRP and WIfI amputation score but negatively correlated with ABI (p<0.001).
Conclusion: Serum Elabela level, which is known to be increased in inflammatory processes, has the potential in predicting low extremity arterial obstruction and WIfI amputation risk in LEAD patients.
Key words: Elabela, lower extremity arterial disease, inflammation

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Introduction

The cardiovascular system is influenced by many systemic and local bioactive peptides and neural and hormonal systems. The renin-angiotensin-aldosterone (RAA) system, sympathetic nervous system, parasympathetic nervous system, and natriuretic peptide system are well-known and previously investigated systems, which are interrelated and often activated to protect the cardiovascular condition and can be used in the diagnosis and treatment of cardiovascular diseases (1).

The G protein-coupled apelin receptor (APJ) and its cognate ligand, apelin, are widely expressed throughout the human body. They are implicated in different key physiological processes, such as angiogenesis, cardiovascular functions, fluid homeostasis, and energy metabolism regulation (2). The APJ receptor has 31% similarity to the final receptor of the RAA system, angiotensin II type 1A receptor. Recently, a new endogenous peptide ligand of APJ, named Elabela, has been identified. Elabela and apelin antagonize the RAA system, therefore playing a crucial role in preventing cardiovascular disease and slowing disease progression (3). In recent studies, apelin and these related peptide receptors have been shown to have cardioprotective effects in atherosclerosis and myocardial infarction (MI), heart failure (HF) (4), and pulmonary arterial hypertension (5). Elabela and apelin antagonize the RAA system in HF patients, reduce remodeling, increase myocardial

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HIGHLIGHTS

- Elabela is a ligand of the APJ receptor, antagonize the RAA system, therefore playing a crucial role in preventing cardiovascular disease.
- LEAD significantly increases the risk of death; whereas advanced ischemic changes very often contribute to amputation of the lower limb.
- Elabela level has the potential in predicting arterial obstruction and amputation risk in LEAD patients.

vascularity, cause peripheral vasodilation, increase cardiac output, and are therefore considered to play a very important role in preventing cardiovascular disease (6) and slowing disease progression in HF patients (7).

In the present study, we aimed to investigate the serum Elabela levels in lower extremity arterial disease (LEAD) and reveal the possible relationship between serum Elabela levels and WIfI score, which is a new amputation risk score in LEAD.

Methods

Study population

The study was planned to be a cross-sectional one, including 119 patients who presented to the cardiology clinic with complaints of claudication and who underwent lower extremity peripheral angiography. The patients were categorized based on significant lower extremity artery stenosis in at least one of the infrainguinal major arteries (superficial femoral artery, tibialis anterior artery, peroneal artery, tibialis posterior artery, and tibioperoneal trunk) in both the lower extremities detected by angiography as the LEAD group (n=60, ≥70% luminal stenosis or total occlusion) and the control group (n=59, ≤30% luminal stenosis).

Two cardiologists reviewed the angiographic images in a double-blinded manner. The ratio of the stenotic segment to normal segment diameter was determined using the QCA system. Additionally, the LEAD group was divided into subgroups according to the Rutherford classification (8). Ankle-brachial index (ABI) was measured, and patients were examined in detail with many variables, such as the presence of an ischemic foot injury, which is a term used to describe conditions, such as minor tissue loss due to peripheral artery disease of the lower extremities, non-healing ulcer, or gangrene. WIfI amputation risk score was calculated and recorded (8).

Patients over the age of 85, under the age of 18, with known moderate-to-severe valvular disease, chronic liver and kidney disease (GFR <60 mL/kg/min), active infectious diseases, autoimmune disease, coagulopathy, malignancies, who received immunosuppressive treatment, and with acute aortic and coronary syndromes, acute cardiac conduction disorders, and decompensated HF were excluded in our study.

All patients and controls were questioned about demographic variables and were enrolled consecutively. They were also examined in detail by a specialist physician from the internal medicine clinic for chronic diseases. Hypertension was defined as a systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or current use of antihypertensive medication (9). Diabetes mellitus was defined as a fasting serum glucose ≥126 mg/dL, hemoglobin A1C ≥6.5%, or the use of blood glucose-lowering agents (10). The American Society of Echocardiography standards were used for all measurements. HF was defined as <50% systolic ejection fraction (11). The study was approved by the Local Ethics Committee of Çukurova University, with signed written informed consent forms from all subjects for the study.

Laboratory parameters

Laboratory analyses, such as glucose, high-sensitive troponin I, creatinine kinase myocardial band (CK-MB), N terminal pro-brain natriuretic peptide (NT-ProBNP), renal functions, lipid parameters, high-sensitivity C-reactive protein (Hs-CRP), and complete blood count, were analyzed and recorded from routine blood tests. All blood analyses were conducted by the same laboratory with the same device (Roche Hitachi System, Switzerland) by the same trained staff using the same methodology. Serum Elabela levels were determined using commercial kits (Sunred Biological Technology, Shanghai, China). Elabela–32 isoform was measured. The kit used a double-antibody sandwich enzyme-linked immunosorbent assay to evaluate the Elabela level in samples. According to the manufacturer, this assay has <12% and <10% inter-assay and intra-assay coefficients of variation, respectively. All of the above tests were performed from blood samples, which were taken at the 24th hour of hospital admission.

Statistical analysis

Statistical analyses were conducted using SPSS 23 for Windows (SPSS Inc., Chicago, IL, USA). The distribution of data was investigated using the Kolmogorov-Smirnov or Shapiro-Wilk test. Continuous variables, according to the presence or absence of normal distribution, were expressed as mean ± standard deviation or median ± quartile deviation, respectively. Categorical variables, on the other hand, were expressed as percentages. Comparing between LEAD and control groups, chi-square test, independent t-test, or Mann-Whitney U test was used. Elabela and Hs-CRP values in subgroups were compared by independent t-test, Mann-Whitney or Kruskal-Wallis test. Additionally, they also were evaluated according to Rutherford classes by the Kruskal-Wallis test. To determine which Rutherford classes are different from each other in terms of Elabela and Hs-CRP, the Dunn-Bonferroni test conducted pairwise comparison. Besides, in the LEAD groups, correlations between Elabela, Hs-CRP, WIfI, and ABI were demonstrated by scatter plots, and Spearman Rho correlation coefficient was calculated. Lastly, the ROC curve analysis was applied to Elabela, and the cutoff point for LEAD and control groups was determined by the Youden J index. In all analyses, two-tailed $p<0.05$ was considered statistically significant.

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Results

There were two groups in our study: patients with significant LEAD (group 1) and the control group (group 2). No statistically significant difference was found between the LEAD and control groups in terms of sex and cardiovascular risk factors, including diabetes mellitus, hypertension, and smoking. Table 1 shows baseline demographic characteristics and laboratory findings of the groups. Serum low-density lipoprotein (LDL), Elabela, and Hs-CRP levels were statistically higher in the LEAD group (p=0.002, p<0.001, and p<0.001, respectively). Other laboratory parameters were similar (Table 1).

The LEAD group was divided into groups according to the Rutherford classification, with Table 2 showing the serum Elabela and Hs-CRP levels in this classification. It is noteworthy that serum Elabela and Hs-CRP levels increase in a correlated manner as the classification stage increases. Figure 1 and Table 3 show pairwise comparisons of Elabela and Hs-CRP according to the Rutherford classification.

Table 1. Baseline demographic properties and biochemical variables of groups

Demographic properties	LEAD (n=60)	Control (n=59)	*P*-value
Age (years, mean)	59±7.8	57.4±8.6	0.121
Sex (Female, %)	19 (31.7%)	26 (44.1%)	0.163
Hypertension (n, %)	34 (58%)	43 (72.9%)	0.134
Diabetes mellitus (n, %)	38 (63.3%)	40 (67.8%)	0.608
Smoking (n, %)	39 (65%)	39 (66.1%)	0.899
Heart failure (n, %)	9 (15%)	11 (18.6%)	0.595
History of PCI (n, %)	7 (11.7%)	4 (6.8%)	0.357
History of CABG surgery (n, %)	6 (10%)	4 (6.8%)	0.527
Chronic obstructive lung disease (n, %)	9 (15%)	11 (18.6%)	0.595
Biochemical variables			
Hemoglobin (g/dL)	13.7±2.2	13.3±1.4	0.198
Leukocyte (×10^3/μL)	8.5±1.8	8.4±2.5	0.765
Platelet (×10^3/μL)	283±91	271±49	0.401
Plasma fasting glucose (mg/dL)	112.5±65.8	121±57	0.180
Creatinine (mg/dL)	0.8±0.22	0.77±0.17	0.333
Low-density lipoprotein (mg/dL)	162.5±86	147±32	0.002*
High-density lipoprotein (mg/dL)	34±11.5	44.6±8.3	0.887
Aspartate aminotransferase (IU/L)	15.5±7.4	16.7±6.7	0.512
Alanine aminotransferase (IU/L)	17±8.3	17.6±9.4	0.432
Brain natriuretic peptide (pg/mL)	17±8.75	16±10	0.312
Hs-CRP (mg/L)	7.4±3.7	2.5±2.1	<0.001*
Elabela (ng/mL)	2.8±1.9	0.92±1.7	<0.001*

*P<0.05 is significant.
CABG - coronary artery bypass graft surgery; PCI - percutaneous coronary intervention; LEAD - lower extremity arterial disease; Hs-CRP - high-sensitivity C-reactive protein

The Elabela levels were observed to differ in the LEAD group according to the lesion location. They were higher in significant stenoses than the control group (p<0.001); other groups (SFA, TAA, TPA, PA) were seen to not differ from each other (Table 4). In subgroup analyses, the Elabela level was found to not be affected by

Table 2. Rutherford classification, Elabela, and high-sensitivity C-reactive protein values

LEAD classification	Elabela (ng/mL)	Hs-CRP (mg/L)
Rutherford class 0 (n=59)	0.91±1.6	1.7±0.9
Rutherford class 1 (n=9)	2.0±0.8	1.8±0.7
Rutherford class 2 (n=14)	2.3±2.1	2.8±1.9
Rutherford class 3 (n=14)	2.4±2.1	3.5±2.4
Rutherford class 4 (n=8)	3.7±2.0	5.8±2.7
Rutherford class 5 (n=8)	4.±0.5	15.2±6.7
Rutherford class 6 (n=7)	5.1±2	24.2±6.7
P-value	<0.001*	<0.001*

**P*<0.05 is significant. LEAD - lower extremity arterial disease; Hs-CRP - high-sensitivity C-reactive protein

Table 3. Pairwise comparisons of Elabela and high-sensitivity C-reactive protein according to Rutherford classes

Pairwise comparisons	*P*-value [Elabela (ng/mL)]	*P*-value [Hs-CRP (mg/L)]
Class 0 – Class 1	0.228	1.000
Class 0 – Class 2	0.007*	0.604
Class 0 – Class 3	0.354	1.000
Class 0 – Class 4	0.003*	1.000
Class 0 – Class 5	<0.001*	<0.001*
Class 0 – Class 6	<0.001*	<0.001*
Class 1 – Class 2	1.000	1.000
Class 1 – Class 3	1.000	1.000
Class 1 – Class 4	1.000	1.000
Class 1 – Class 5	0.836	0.004*
Class 1 – Class 6	1.000	<0.001*
Class 2 – Class 3	1.000	1.000
Class 2 – Class 4	1.000	1.000
Class 2 – Class 5	0.987	0.289
Class 2 – Class 6	1.000	0.088
Class 3 – Class 4	1.000	1.000
Class 3 – Class 5	0.143	0.010*
Class 3 – Class 6	0.237	0.002*
Class 4 – Class 5	1.000	0.263
Class 4 – Class 6	1.000	0.089
Class 5 – Class 6	1.000	1.000

**P*<0.05 is significant. Hs-CRP - high-sensitivity C-reactive protein

Table 4. Elabela values for subgroups

Parameter	Subgroups	Elabela (ng/mL)	*P*-value	Hs-CRP (mg/L)	*P*-value
Lesion localization	None (n=59)	0.9±0.8	<0.001*	1.7±1	<0.001*
	SFA (n=27)	3.4±1.7		2.6±6	
	TAA (n=15)	3±1.5		4±3.3	
	TPA (n=10)	2.7±2.2		2.2±4.4	
	PA (n=8)	2.6±1.7		2.1±1.8	
Hypertension	(Yes) (n=77)	2.5±1.5	0.300	2±1.8	0.563
	(No) (n=42)	2.3±1.3		2.3±2.5	
Diabetes mellitus	(Yes) (n=78)	2.2±1.5	0.991	2.6±2.4	0.100
	(No) (n=41)	2.3±1.3		2±1.1	
Smoking	(Yes) (n=78)	2.3±1.5	0.313	2.1±2.1	0.811
	(No) (n=41)	2.2±1.5		2.3±1.7	
Heart failure	(Yes) (n=20)	2.2±1.5	0.333	2.7±2.4	0.154
	(No) (n=99)	2.1±1.6		2±1.4	
Ischemic foot injury	(Yes) (n=15)	4.5±1.5	<0.001*	20±5	<0.001*
	(No) (n=104)	1.6±0.9		2.3±1.7	
ABI	ABI (normal, >0.9) (n=49)	0.9±1.1	<0.001*	1.4±1	<0.001*
	ABI (mild, 0.8–0.9) (n=24)	2.3±1.8		2.2±0.5	
	ABI (moderate, 0.5–0.8) (n=42)	3±1.5		4±4.1	
	ABI (severe, <0.5) (n=4)	4.5±2.8		22.9±16.8	

*$P<0.05$ is significant. ABI - ankle-brachial index; SFA - superficial femoral artery; TAA - tibialis anterior artery; TPA - tibialis posterior artery; PA - peroneal artery; Hs-CRP - high-sensitivity C-reactive protein

Table 5. Correlations of variables

Variables	r-value	*P*-value
Elabela and Hs-CRP	0.644	<0.001*
Elabela and WIfI	0.453	<0.001*
Elabela and ABI	-0.446	<0.001*
Hs-CRP and WIfI	0.581	<0.001*

*$P<0.05$ is significant. ABI - ankle-brachial index; Hs-CRP - high-sensitivity C-reactive protein

these variables in hypertensive, diabetes, smoking, and HF groups, but the Elabela level was significantly higher in groups with an ischemic foot injury ($p<0.001$). In the investigations made according to the ABI classification, it is noteworthy that the Elabela level increases as the ABI rate decreases (Table 4).

In the correlation analyses, including the LEAD group, the Elabela level was statistically found to be positively correlated with Hs-CRP and WIfI risk score but negatively correlated with ABI ($p<0.001$). Also, the positive correlation between WIfI risk score and Hs-CRP levels was remarkable ($p<0.001$). Figure 2 shows the scatter plots of Elabela, ABI, WIfI, and Hs-CRP, and Table 5 shows the correlation analysis results.

In the ROC analysis, a cutoff value of ≥1.225 serum Elabela level had an 88.2% sensitivity and 69% specificity for predicting LEAD [area under the curve (AUC): 0.798, 95% CI 0.717–0.879, $p<0.001$] (Fig. 3).

Discussion

The most important finding of our study was the significant increase of serum Elabela value in LEAD patients. Our study is the first literature examining the relationship between serum Elabela level and ischemic foot injury/WIfI amputation risk score in LEAD. As the stage increased according to the Rutherford classification, serum Elabela levels also increased. It would be more accurate to state that the Elabela has the potential to predict low extremity arterial obstruction, which is more pronounced in Rutherford 5 and 6, where the severity of the disease increases; Elabela and Hs-CRP were relatively higher.

In the current ESC Peripheral Arterial Guideline, the novel risk score and WIfI classification should be used to show the risk of amputation (8). Similarly, serum Elabela levels correlated positively with WIfI score. It is noteworthy that the Elabela level, which is an inflammatory marker, is positively correlated with Hs-CRP and WIfI score and negatively correlated with ABI, which indicates disease severity.

Apelin and Elabela are ligands of the APJ receptor. The coupling of this receptor and its ligands plays some regulatory roles in the cardiovascular, central nervous, circulatory, and many other systems. Apelin is widely distributed in the human body, while Elabela is found in plasma. Its expression is highest in the embryonic heart tissue, and after that, it declines gradually. Elabela is mainly detected in the fibroblasts and endothelial cells

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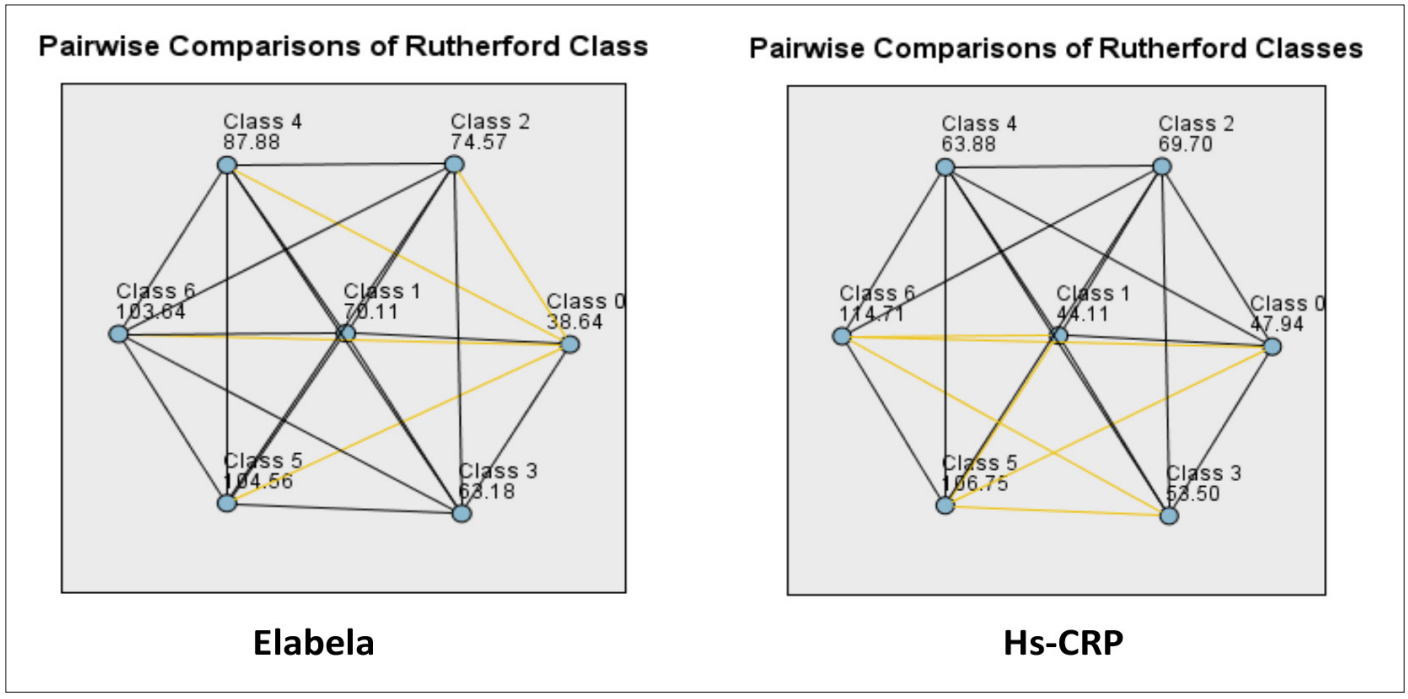

Figure 1. Pairwise comparisons of Elabela and high-sensitivity C-reactive protein according to Rutherford classes, respectively (each node shows the sample average rank of Rutherford classes, and yellow lines represent the statistically significant difference between the two classes)

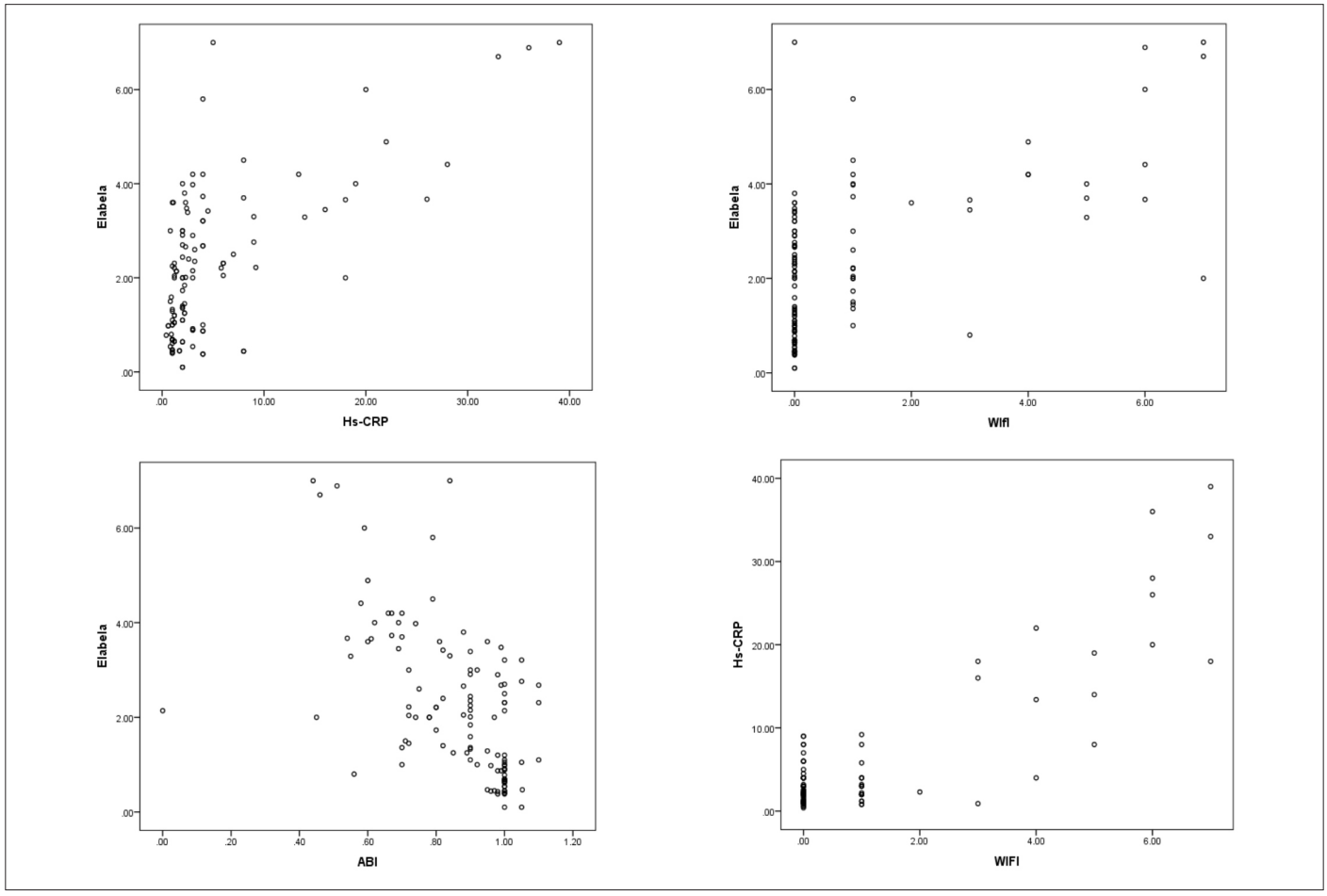

Figure 2. Scatter plots of Elabela, ankle-brachial index, WIfI, and high-sensitivity C-reactive protein

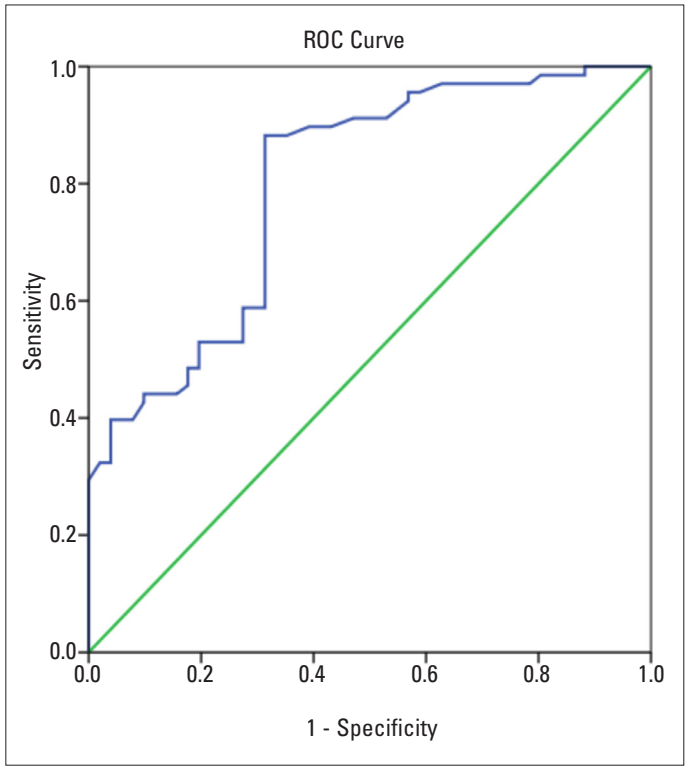

Figure 3. ROC curve of Elabela. AUC=0.798, cutoff value 1.225, 88.2% sensitivity, 69% specificity
AUC - area under the curve; ROC - receiver operating characteristic

of the heart, which is essential for the normal development of the heart tissue (12).

Studies on the effects of apelin and Elabela on the cardiovascular system showed that they (1) contribute to the formation of heart and angiogenesis in the embryogenic period, (2) have inotropic effects, (3) cause reduction or deceleration in diseases causing cardiac hypertrophy and fibrosis, and (4) improve HF and MI clinic (13).

The apelinergic system is an important peptide family in HF patients but is not well-known as much as other systems. To the best of our knowledge, an increase in apelin levels occurs in HF patients. In the previous study, the serum apelin level was shown to increase the intracellular calcium level in systolic HF patients, and they reported that the serum apelin level was high and decreased in the early period of the patients and later stages of heart failure, respectively (14).

Circulating Elabela may act directly on maternal endothelial cells, promoting vasodilation and regulating diuresis and fluid balance. Recently, Ho et al. (15) proposed decreased placental release of Elabela as a causal factor in preeclampsia. Deletion of the murine Elabela gene caused preeclampsia-like symptoms with proteinuria, hypertension, and kidney injury during pregnancy. They proposed that the loss of Elabela perturbs early placental vascular development, resulting in an inadequately perfused placenta. Ho et al. (15) showed that Elabela may have paracrine roles in placental development, acting on fetal endothelial cells to facilitate normal branching angiogenesis and formation of the labyrinth network, allowing proper placental exchange. Elabela-knockout mice showed preeclampsia-like symptoms, such as hypertension, proteinuria, etc., and these mice can return to normal after the infusion of exogenous Elabela.

Severe preeclampsia and early-onset preeclampsia are believed to be secondary features of a primary placenta disorder. The Elabela plasma levels in severe or early-onset preeclampsia women or in pregnant women in general more likely reflect the mixed maternal and placental contributions. And it seems unlikely that Elabela can serve as a biomarker for preeclampsia. However, these studies strongly support the hypothesis that Elabela is implicated in preeclampsia, as no evidence exists yet that Elabela levels are reduced in human disease (16).

Currently, the information regarding the role of Elabela in MI is based on animal models. Perjés et al. (3) demonstrated a substantial increase in Elabela expression (6.6-±2.3-fold increase in MI group vs. sham, $p<0.05$) and APJ receptor (1.8-±0.3-fold increase in MI group vs. sham, $p<0.05$) in rat left ventricle samples. They also observed a high correlation between Elabela and APJ receptor expression. In another rat study, Rakhshan et al. (17) documented Elabela's cardioprotective effects. MI was induced and 5 µg/kg Elabela was administered intraperitoneally to rats for 4 days. They showed that CK-MB, troponin I levels, oxidative stress markers, and infarct size were significantly decreased in the Elabela treatment group. And in one recent human study, Dönmez and Acele (18) showed a significant increase of Elabela levels in both anterior and inferior ST-elevation MI patients.

Worldwide, over 200 million people are diagnosed with LEAD (11). Major risk factors for the development of LEAD include age, smoking, hypertension, diabetes, dyslipidemia, and a history of cardiovascular disease (19). Evaluation of the clinical stage of the LEAD is recommended to be conducted according to the Fontaine and Rutherford classification in line with the current guidelines (8). We did our clinical staging according to Rutherford. As the clinical stage increased, the serum Elabela level also increased.

LEAD significantly increases the risk of death; whereas advanced ischemic changes very often contribute to amputation of the lower limb (20). Chronic limb treating ischemia entity includes clinical patterns with a threatened limb viability related to several factors. The three primary factors that constitute and contribute to the risk of limb threat are wound (W), ischemia (I), and foot infection (fI) (21). A new classification system (WIfI) has been proposed to initially assess all patients with ischemic rest pain or wounds (22). Based on this data, it was stated that WIfI classification should be used to show the risk of amputation (23). In our study, we calculated the WIfI score in the LEAD group and found it to positively correlate with the serum Elabela level and Hs-CRP. The relationship between Hs-CRP level and inflammatory processes is known in the literature. It is also noteworthy that a strong correlation exists between the WIfI score and serum Elabela level.

The ABI, the ratio of lower extremity blood pressure to upper extremity blood pressure, is a simple and convenient method used to diagnose LEAD, which is a local manifestation

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of systemic atherosclerosis. An ABI of 0.9 has been shown to have a high sensitivity (90%–97%) and specificity (98%–100%) for detecting LEAD (24). Its sensitivity is poorer in diabetes or end-stage chronic kidney disease patients because of medial calcification (8). Therefore, it has been widely used as a screening index for LEAD. The ABI is associated with the increased risk of cardiovascular disease, cardiovascular mortality, and all-cause mortality (25). We classified our patients according to the ABI data. It is noteworthy that the Elabela level increases as the ABI rate decreases, supporting the role of inflammation in LEAD.

Study limitations

The main limitations of our study are the cross-sectional design and sample size. Apelin and APJ measurements would have provided more details on the apelinergic system in LEAD patients.

Conclusion

In conclusion, the serum Elabela level, which is known to be increased in inflammatory processes, has the potential in predicting low extremity arterial obstruction and amputation risk in LEAD patients.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

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