ORIGINAL ARTICLE

Evaluation of Elabela Levels in Obese Individuals

OBEZ BIREYLERDE ELABELA DÜZEYLERİNİN DEĞERLENDİRİLMESİ

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ABSTRACT

Objective: Obesity is a condition that occurs as a result of excessive weight gain. Obesity is related with the high risk of several diseases like cardiovascular diseases and diabetes mellitus. Elabela is a peptide that has emerged recently and is known to affect food intake by binding to apelinergic receptors. This study aimed to investigate the serum levels of Elabela in obese and non-obese individuals.

Material and Methods: This study involved 24 people with obesity and 25 healthy adult people as control group. Height, weight, gender, age, waist-hip circumference, blood pressure of participants were recorded and routine blood tests were measured. Serum concentrations of Elabela were determined using enzyme-linked immunosorbent assay.

Results: When comparing the obese group to the controls, no statistically significant differences were observed between the two groups in terms of diastolic blood pressure, blood urea nitrogen, creatinine, total cholesterol, low density lipoprotein cholesterol and C-reactive protein. Similarly, both groups did not differ statistically regarding Elabela levels. The obese group exhibited significantly elevated levels of body mass index, waist/hip ratio, systolic blood pressure values, glucose, aspartate aminotransferase, alanine aminotransferase, triglyceride, insulin, homeostatic model assessment for insulin resistance (HOMA-IR) compared to the control group. The obese group demonstrated a significantly lower level of high-density lipoprotein cholesterol in comparison to the control group.

Conclusion: In this study, it was found that there was no relationship between Elabela levels and obesity. However, this issue needs to be supported by further studies to clarify.

Keywords: *Apelinergic Receptor; Obesity; Elabela*

ÖZET

Amaç: Obezite aşırı kilo artışı sonucu ortaya çıkan bir durumdur ve kardiyovasküler hastalık riskinde artış, diyabet oluşumunda artış gibi pek çok hastalıkla ilişkilidir. Elabela son zamanlarda ortaya çıkan ve apelinerjik reseptörlere bağlanarak yiyecek alımı üzerine etki gösterdiği bilinen peptit yapılı bir hormondur. Bu çalışmanın amacı obez ve obez olmayan bireylerde serum Elabela düzeylerini araştırmaktır.

Gereç ve Yöntemler: Bu çalışmaya 24 obez ve kontrol grubu olarak 25 sağlıklı erişkin birey dahil edildi. Tüm katılımcıların boy, kilo, cinsiyet, yaş, bel-kalça çevresi, kan basıncı değerleri kaydedildi ve rutin kan testleri çalışıldı. Serum Elabela düzeyleri enzim ilişkili immünosorbent yöntemle ölçüldü.

Bulgular: Obez grup ile kontroller karşılaştırıldığında iki grup arasında diyastolik kan basıncı, kan üre nitrojeni, kreatinin, total kolesterol, düşük yoğunluklu lipoprotein kolesterol ve C-reaktif protein açısından istatistiksel olarak anlamlı bir fark gözlenmedi. Benzer şekilde her iki grupda Elabela düzeyleri açısından istatistiksel olarak farklılık bulunmadı. Obez grupta kontrol grubuyla karşılaştırıldığında vücut kütle indeksi, bel/kalça oranı, sistolik kan basıncı değerleri, glukoz, aspartat aminotransferaz, alanin aminotransferaz, trigliserit, insülin, insülin direnci için homeostatik model değerlendirmesi (HOMA-IR) değerlerinde anlamlı düzeyde artış görüldü. Obezlerde, yüksek yoğunluklu lipoprotein kolesterol seviyesi kontrol grubuna göre anlamlı düşük bulundu.

Sonuç: Bu çalışmada Elabela düzeyleri ile obezite arasında bir ilişki olmadığı görüldü. Fakat bu konunun netliğe kavuşması için daha ileri çalışmalarla desteklenmesi gerekmektedir.

Anahtar Kelimeler: *Apelinerjik Reseptör; Obezite; Elabela*

INTRODUCTION

Obesity is defined as a multisystem disease in which genetic - environmental factors and lifestyle play a role (1). It can lead to many ailments, including cardiovascular disease, type 2 diabetes, high blood pressure, stroke, diverse forms of cancer, and mental well-being. According to the World Health Organization's (WHO) 2022 statistics, over 1 billion individuals worldwide are afflicted by obesity, including 650 million adults, 340 million adolescents, and 39 million children. It is foreseen that there will be serious increases in these numbers in a near future (2).

The apelinergic system comprises the apelin receptor (APJ/APJR) and the natural ligands for this receptor, namely Apelin and Elabela (also recognized as APJ early endogenous ligand, Apela, Toddler, Ela). The APJ receptor has been demonstrated to exert diverse physiological impacts on the control of fluid balance, food consumption, glucose metabolism, cardiovascular function regulation, angiogenesis, cardiac development, cardiac contractility, vascular tone, cardiac hypertrophy, type 2 diabetes, and obesity (3–5).

Elabela is a peptide hormone found after Apelin and acts by binding to apelinergic receptors. It was first described by Reversade's group as the first ligand of APJ in zebrafish embryos and shown to have effects on endodermal differentiation and cardiogenesis. Elabela is primarily present in embryonic stem cells, vascular endothelium, kidney, prostate tissue, and placenta. Elabela is similar to apelin, both bind to the same receptor APJ and cause similar effects (3). Although they have similar effects, these two peptides differ from each other in that they employ distinct signaling pathways and induce diverse biological effects. Additionally, there have been reports indicating that Elabela produces its effects via a receptor other than the APJ receptor (6). Elabela regulates vascular and cardiac functions in adults , stimulates angiogenesis, relaxes mouse aortic blood vessel and exerts anti-hypertensive effect , inhibits renal remodeling, inhibits fibrosis , and also has effects on water homeostasis (7-11). Apart from these, it has been established that Elabela has anorexigenic (appetite-reducing) impact in mouse)(12). In the literature, although there are studies examining the relationship of Apelin with obesity, there is no clinical study investigates the relationship of Elabela with obesity. In the present study, our objective was to examine whether there is a difference between serum Elabela levels in obese individuals compared to the normal population and to evaluate the role of Elabela in obesity.

MATERIALS AND METHODS

Subjects

This study is a cross-sectional case-control study conducted at the Department of Internal Medicine and Medical Biochemistry, Yozgat Bozok University Faculty of Medicine between 2021-2022. Twenty-four adults (18-56 years) diagnosed with obesity (body mass index (BMI) ≥30 kg/m2) (obese group), and 25 age- and sex-matched healthy volunteers without obesity (BMI<25 kg/m2) (control group) were involved in this study. Height, weight, waist circumference, hip circumference, systolic blood pressure (SBP) and diastolic blood pressure (DBP) measurements were made for all participants. Waist/hip circumference ratios were calculated. Smoking habits and alcohol use were questioned. All demographic data were recorded.

Individuals with a history of recent surgery or trauma, lactation, pregnancy, lipid-lowering drug use, chronic drug use (prescription/nonprescription), chronic disease (including cardiovascular disease, hypertension, diabetes mellitus, chronic infections, chronic kidney disease, malignancy) were not included in the study.

This study was performed under the ethical standards outlined by the Declaration of Helsinki and received approval from the Yozgat Bozok University Clinical Research Ethics Committee (Approval number: 2017-KAEK-189-2021.04.28-04). All the individuals included in the study were briefed about the study, and their informed written consent was obtained.

Methods

Blood samples from all individuals in the study were taken between 08:00 and 10:00 in the morning after at least 10 hours of fasting, into yellow capped gel tubes. The venous blood samples were centrifuged at 4000 rpm throughout 10 minutes at +4°C to obtain serum. Routine laboratory parameters were studied in serum. For the Elabela measurement, the remaining serum samples were stored at -80°C till the day of analysis.

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Measurement of glucose, blood urea nitrogen (BUN), creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total cholesterol, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), triglyceride and C-reactive protein (CRP) levels in Roche Cobas® 6000 c501 (Roche Diagnostics GmbH, Manheim, Germany) biochemistry autoanalyzer, insulin levels were determined in Roche Cobas® 6000 e601 (Roche Diagnostics GmbH, Manheim, Germany) immunoassay autoanalyzer. Homeostatic model assessment of insulin resistance (HOMA-IR) was calculated according to the formula (13):
HOMA-IR=(Glucose (mg/dL)x Insulin (mU/L))/405
Human Elabela ELISA kit (Bioassay technology laboratory Shanghai, China, Lot number: 202205002) was used to measure serum Elabela levels. This kit is a competitive kit used for the quantitative determination of Elabela in serum. As indicated by the kit manufacturer, the coefficient of variation (CV) for intra-assay was less than 10%; for inter-assay, it was less than 12%, and the sensitivity was 0.00713 ng/mL.

Statistical Analysis

The conformity of the data obtained from the groups to the distribution was evaluated with the Shapiro-Wilk test. Comparisons between categorical data were made using the chi-square test. Comparisons between groups for normally distributed numeric variables were evaluated using the independent samples t-test, and for numeric variables not normally distributed, intergroup comparisons were evaluated with the Mann-Whitney U test. Calculated results were presented as mean ± standard deviation for tests that followed a normal distribution, and as median (min-max) for variables that did not conform to a normal distribution. The number of participants in the groups was expressed as 'n' in the tables. Relationships between numerical variables were evaluated with Spearman's Rank correlation coefficient. A value of $p<0.05$ was considered statistically significant. The data obtained from the study were evaluated with the IBM SPSS Statistics 26.0 (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp) package program.

RESULTS

A total of 49 individuals, 24 obese (12 female, 12 male) and 25 healthy controls (19 female, 6 male) were included in this study. The mean age values of obese and control groups were 37.25 ± 7.37 and 32.8 ± 9.1 years, respectively. Any significant differences were not found between the groups in terms of average age, gender differences, DBP and smoking. SBP, BMI and waist/hip ratio were significantly higher in obese group (Table 1). Glucose, AST, ALT, triglyceride, CRP, insulin, HOMA-IR values exhibited a significant increase in the obese group once again, and HDL-C levels were lower. No statistically significant differences were observed

Table 1. Demographic data of the obese and control groups

Variables	Obese (n=24)	Control (n=25)	p-Value
Age (years)	37.25 ± 7.37	32.8 ± 9.1	0.067
Gender Female Male	 12 (50%) 12 (50%)	 19 (76%) 6 (24%)	0.112
SBP (mmHg)	120.00 (90-130)	100.00 (95-130)	0.025*
DBP (mmHg)	80.00 (60-85)	70.00 (60-85)	0.129
BMI (kg/m^2)	34.55 (30.37-54.03)	21.71 (17.1-24,91)	<0.001**
Waist/hip ratio	0.89 (0.74-1.12)	0.83 (0.71-1.17)	0.026*
Smoking (≥5 pcs/day)	 3 (12.5%)	 2 (8%)	0.667

* p<0.05, **p<0.01 Data are shown as mean ± standard deviation, median (min-max) and percentage. SBP: systolic blood pressure, DBP:diastolic blood pressure, BMI: body mass index

between the groups regarding BUN, creatinine, total cholesterol, LDL-C and Elabela levels (Table 2). No correlation was found between Elabela and numerical variables. Table 3 presents the outcomes of the correlation analysis conducted among numerical variables.

Table 2. Laboratory findings of the obese and control groups

Variables	Obese n=24	Control n=25	p-Value
Glucose (mg/dL)	94.02 ± 7.88	86.36 ± 6.10	<0.001**
BUN (mg/dL)	12.28 ± 3.12	11.11 ± 2.86	0.177
Creatinine (mg/dL)	0.75 ± 0.11	0.72 ± 0.12	0.437
AST (U/L)	16.55 (10.0-39.9)	14.20 (10.1-20.8)	0.026*
ALT (U/L)	18.35 (10.7-36.2)	11.5 (5.9-28.0)	<0.001**
Total cholesterol (mg/dL)	170.15 (126.9-225.2)	161.1 (121.5-200.0)	0.522
Triglyceride (mg/dL)	111.1 (26.1-246.8)	81.0 (32.9-199.3)	0.002*
HDL-C (mg/dL)	42.85 ± 10.02	55.44 ± 12.89	<0.001**
LDL-C (mg/dL)	100.22 (60.04-159.5)	95.14 (64.06-125.6)	0.222
CRP (mg/L)	2.67 (0.6-13.49)	1.28 (0.6-4.01)	0.005*
Insulin (mU/L)	16.9 (4.5-61.6)	7.9 (2.6-14.8)	<0.001**
HOMA-IR	3.9 (0.89-15.69)	1.7 (0.51-3.07)	<0.001
Elabela (ng/mL)	0.58 ± 0.37	0.55 ± 0.30	0.744

* p<0.05, **p<0.01 Data are shown as mean ± standard deviation and median (min-max). BUN: blood ure nitrogen, AST: aspartate aminotransferase, ALT: alanine aminotransferase, HDL-C: high density lipoprotein-cholesterol, LDL-C: low density lipoprotein-cholesterol, HOMA-IR: Homeostasis Model Assesment-insulin resistance

Table 3. Correlation Analysis Between Numerical Variables

	Age	BMI	SBP	DBP	Waist/hip	Glucose	BUN	Creatinine	AST	ALT	Cholesterol	Triglyseride	HDL	LDL	Insulin	CRP	HOMA-IR
Age																	
BMI	0.13																
SBP	0.06	.402**															
DBP	-0.027	.283*	.674**														
Waist/hip	0.222	.415**	.360*	0.263													
Glucose	0.22	.322*	0.258	0.157	-0.003												
BUN	0.195	0.169	.304*	0.182	.354*	-0.022											
Creatinine	.396**	0.211	0.28	0.093	.482**	0.01	.476**										
AST	.327*	0.195	0.03	-0.061	-0.121	.459**	0.092	0.146									
ALT	.312*	.490**	0.221	-0.019	0.267	.475**	0.242	.358*	.574**								
Cholesterol	.344*	0.04	-0.041	-0.236	0.045	0.033	0.075	0.155	.393**	.342*							
Triglyseride	.478**	.340*	0.159	0.001	0.131	0.247	0.113	.398**	.414**	.405**	.443**						
HDL	-0.211	-.479**	-.362*	-.318*	-.358*	-.372**	-0.065	-0.269	0.047	-0.176	.342*	-.409**					
LDL	.468**	0.157	0.034	-0.168	0.245	0.094	0.108	0.202	.326*	.398**	.895**	.389**	0.069				
Insulin	-0.046	.648**	.356*	0.229	0.134	.541**	0.088	0.091	.330*	.533**	0.061	0.243	-.315*	0.051			
CRP	0.087	.546**	0.181	0.205	0.257	0.085	0.007	0.079	0.029	.340*	-0.041	0.001	-0.163	0.137	0.271		
HOMA-IR	-0.019	.626**	.376**	0.241	0.112	.627**	0.062	0.08	.363*	.553**	0.058	0.263	-.346*	0.056	.990**	0.269	
Elabela	-0.027	-0.001	-0.232	0.032	-0.238	0.082	-0.157	-0.114	0.124	0.044	-0.163	-0.066	-0.028	-0.168	0.066	0.267	0.083

* p<0.05, **p<0.01, BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, BUN: Blood ure nitrogen, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, HDL: High density lipoprotein, LDL: Low density lipoprotein, CRP: C_reactive protein, HOMA-IR: Homeostasis model assesment-insulin resistance

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DISCUSSION

The development mechanism of obesity, which is defined as a multisystemic disease and seen as a contemporary disease, has not yet been fully understood. Studies on the causes of obesity and the development of new treatment strategies are still ongoing and remain popular. In this study, the levels of Elabela, which were shown to be effective on appetite, biochemical parameters and the relationship between them were investigated in obese individuals.

Around 60-70% of individuals with obesity experience dyslipidemia. Irregularities in lipid levels commonly observed in obese individuals are increased triglyceride, very low-density lipoprotein cholesterol, Apo B and non-HDL-C levels. HDL-C and Apo A-I levels are typically low. While LDL-C levels typically fall within the normal range, there is usually a rise in small, dense LDL, leading to an increase in the quantity of LDL particles (14–17). Specifically, obesity in children and young adults is associated with a higher occurrence of elevated triglycerides and reduced levels of HDL-C levels (18). In some studies, obese individuals exhibited elevated levels of total cholesterol, triglycerides, and LDL-C, along with lower levels of HDL-C. (19–21). In this study, consistent with existing literature, the obese group demonstrated elevated triglyceride levels and lower HDL-C levels. However, there were no distinctions between the groups in terms of total cholesterol and LDL-C levels.

Visser et al. showed that as BMI and waist/hip ratio increased, CRP values also increased, that is, CRP was higher in obese individuals. These findings support the presence of low levels of systemic inflammation in obese individuals (22). Similarly, in another study observed elevated serum CRP levels in obese individuals when compared to healthy people. A positive correlation was found between waist circumference and CRP value, and between hip circumference and CRP in the obese group (23). Individuals with acute or chronic infections were not included in our study, and significantly elevated CRP levels were observed in the obese group, and a robust positive correlation existed between BMI and CRP. As stated in the literature, increased CRP levels appear as an indicator of low-level systemic inflammation in obese individuals.

Elabela is synthesized from a 54 amino acid precursor polypeptide. This polypeptide loses its signal sequence and is cleaved to the mature peptide Elabela-32, which consists of 32 amino acids. Further degradation of Elabela-32 yields isoforms such as Elabela-21 and Elabela-11. These isoforms are also functionally active (3). Studies have reported the pleiotropic effects of the apelinergic system and its ligands in many tissues. It plays a role in neuronal protection together with fluid homeostasis in the central nervous system; it decreases atherosclerosis; increases steroidogenesis and proliferation of granulosa cells. Apart from these, it is stated that increases glucose uptake into cells and insulin sensitivity, decreases lipolysis, decreases free radical secretion and plays a role in the pathogenesis of diabetes (24).

In an animal study, Santoso et al., found that intracerebroventricular injection of Rat Ela-21 into adult mice had a reducing effect on food intake. This effect was by activating neurons that synthesize arginine vasopressin and corticotropin-releasing hormone in the paraventricular nucleus (PVN) in the hypothalamus. So Elabela is characterized as a hormone with appetite-suppressing properties that acts on the brain (12). APJ is present in different parts of the central nervous system, including the PVN, which plays a role in the regulation of food intake (25). In addition, it is stated that peripheral Elabela has the capability to penetrate the blood-brain barrier, reaching the central nervous system. (12). Based on the anorexigenic effect of Elabela in mice; we measured serum Elabela levels in obese and healthy individuals. To the best of our knowledge, this study is the first to assess the connection between Elabela levels and obesity. As a result, we determined that there was no difference in serum Elabela levels between obese and healthy individuals. Again, no correlation was found between Elabela levels and other numerical variables. This may be due to the inability of Elabela to adequately cross the blood-brain barrier and not have an effect on nutritional centers in humans. In the study by Santoso et al., the Ela-21 isoform was administered intracerebroventricularly. In this study, the levels of Ela-32, the mature and widely measured isoform of Elabela, were measured. Although both isoforms act on the APJ, there may be differences in affinity for the receptors in the feeding centers. Its isoform may be

Ela-21, which has an effect on food intake, and therefore, no difference in peripheral circulating Ela-32 levels has emerged in obese individuals.

In studies conducted, low levels of Elabela are associated with diabetic nephropathy. In a study by Zhang et al., a negative correlation was shown between the degree of albuminuria and Elabela levels in patients with Type 2 diabetes mellitus (26). Önalan et al. also found that Elabela levels were lower in patients with Type 2 diabetes and associated with the degree of albuminuria; and negative correlated with LDL-C, glucose and BUN levels (27). Obese individuals who do not have a chronic disease such as diabetes or hypertension that may affect Elabela levels were included in this study. The obese group exhibited elevated levels of glucose, insulin, and HOMA-IR values. No correlation was found between Elabela levels and glucose, insulin, HOMA-IR, lipid profile. The relationship of Elabela with glucose metabolism and insulin resistance in non-diabetic individuals needs to be clarified with further studies.

The small number of participants and the fact that only one isoform of Elabela was studied are among the limitations of this study.

CONCLUSION

Although there was no difference in obese individuals in terms of Elabela levels in this study, it would not be correct to reach a definite conclusion owing to the limited participant count. We believe that more valuable information about the role of Elabela in obesity can be revealed with more comprehensive studies with more participants.

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