ORIGINAL ARTICLE

Serum Elabela level is significantly increased in patients with acromegaly

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Abstract

Background Although the bioactive peptides associated with the apelinergic system are known to be associated with heart failure and ischemic heart disease, there are no data on their association with acromegaly.

Aim We aimed to investigate the change in serum Elabela levels, a novel peptide of the apelinergic system, in patients with acromegaly.

Methods Our study included 30 treatment naive patients who were recently diagnosed with acromegaly, and 50 age-and-sex-matched healthy controls. In addition to routine history, physical examination and laboratory examinations, serum Elabela level was measured. Participants were divided into two groups as individuals with and without acromegaly and compared to each other.

Results Diastolic blood pressure (DBP) and systolic blood pressure (SBP) were found to be higher in patients with acromegaly. Serum glucose, Hs-CRP, NT-proBNP, insulin-like growth factor-1, growth hormone and serum Elabela levels were higher in patients with acromegaly ($p < 0.05$ for each). Left ventricular ejection fraction (LV-EF) was found to be lower in patients with acromegaly than the patients in healthy control group ($p < 0.05$). In multivariate analysis; age, systolic blood pressure, NT-proBNP, Insulin-like growth factor 1 and growth hormone levels were found to be very closely and positively related to serum Elabela level ($p < 0.05$ for each).

Conclusions Serum Elabela level can be used as an early and objective indicator of early cardiovascular involvement in patients with acromegaly. Further research is needed to clarify the role of serum Elabela levels on cardiovascular system in acromegaly patients.

Keywords Acromegaly · Apelinergic system · Serum Elabela level

Introduction

Acromegaly is a chronic disease characterized by growth hormone (GH) secreting pituitary adenoma which leads to increased Insulin-like growth factor 1 (IGF-1) synthesis in the liver resulting in excessive protein synthesis and abnormal tissue growth [1]. Chronic high levels of IGF-1 in acromegaly patients cause functional and structural changes specific to the disease [1]. Acromegaly causes left ventricular hypertrophy (LVH), which results in diastolic and systolic dysfunction of the heart [2, 3]. If left untreated, it causes mortality. In patients with acromegaly,

the most common causes of mortality are cardiovascular diseases and malignancies [1, 4].

Apelinergic system has been reported to play an important role in the modulation of the cardiovascular system through the peptide called Apelin and the APJ receptor [5, 6]. Although bioactive peptides associated with the apelinergic system are known to be associated with and protective of heart failure and ischemic heart disease, there are no data on acromegaly patients [7, 8]. Recently, a peptide called Elabela, which binds to the same receptor as Apelin and has similar effects, was found [9]. The positive cardiac effect of Elabela is more prominent than Apelin. Studies have reported that there is a relationship between Elabela and many cardiovascular conditions and diseases. [10]. In patients with acromegaly, elabela level may be an important predictor for the development of cardiovascular

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complications. As far as we have investigated, there is no data on this subject in the literature. Therefore, in our study, it was aimed to investigate the changes in serum Elabela level — a novel apelinergic system peptide — and its relationship with clinical, echocardiographic, and laboratory parameters in patients who were recently diagnosed with acromegaly (Fig. 1).

Methods

This prospective study included 50 patients (31 men, 19 women, and average age 45.1 ± 6.7) who were recently diagnosed with acromegaly and were followed up with that disease, and 50 healthy individuals similar in age and gender as a control group (33 men, 17 women, and average age 44.5 ± 5.3). The duration of the disease before the acromegaly diagnosis was not known. The patients were included in the study before receiving their treatment for acromegaly. Patients who were diagnosed with acromegaly in the primary and secondary health care centers and then referred to our center for treatment were included in the study. The diagnosis and the treatment of acromegaly patients who were included in the study were carried out according to the latest guidelines [1]. Patients with moderately and severely reduced glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 or >30 mg/L proteinuria were excluded. Patients with familial hyperlipidemia, severe and moderate valvular heart disease, known nephrectomy and heart failure history were also excluded. This study was approved by the local ethics committee and conducted according to the recommendations of the ethical principles published in the Declaration of Helsinki developed by the World Medical Association (WMA). All relevant information was explained to the patients in detail, and patients were included in the study after obtaining written consent.

Medical history was taken and detailed physical examinations were performed. Cardiovascular risk factors were noted. Diastolic blood pressure (SBP) and systolic blood pressure (DBP) were measured, and the resting pulse rate was determined. Demographic data including age, sex, hypertension, presence of diabetes mellitus, and history of smoking were recorded. Weight and height of all individuals were measured, and then body mass indexes were calculated.

Laboratory parameters

Routine laboratory parameters [glucose, high-sensitive troponin I, N terminal pro-brain natriuretic peptide
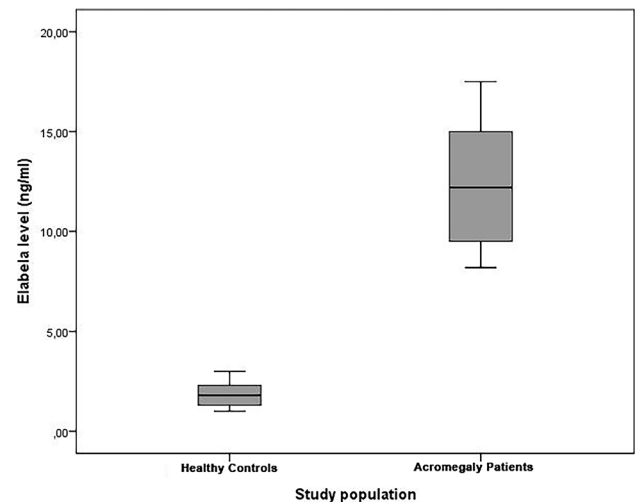
Fig. 1 The Boxplot graphic showed that serum Elabela levels was higher in patients with acromegaly

(NT-ProBNP), renal functions, lipid parameters, high-sensitive C reactive protein (Hs-CRP) and complete blood count] were analyzed from all individuals included in the study. Serum GH level was detected by an automated chemistry analyzer (Abbott Aeroset, MN, USA) using appropriate commercial kits (Abbott) and reference value of GH level was between 0.014 and 5.219 ng/mL. Serum total IGF-1 level was detected by an automated chemistry analyzer (Abbott Aeroset, MN, USA) using appropriate commercial kits (Abbott) and IGF-1 level references value adjusted according to age and sex. Serum IGF-1 and GH levels were measured at the same time with USG examination for each patient with acromegaly.

Serum Elabela levels were measured using commercial kits (Sunred Biological Technology, Shanghai, China). According to the manufacturer; this assay has inter-assay coefficients of variation less than 12% and intra-assay coefficients of variation of less than 10%. Elabela−32 isoform was measured. The kit used a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) to analyze the level of Elabela in samples.

Echocardiographic evaluation

Two-dimensional and Doppler echocardiographic evaluations were performed using an echocardiography device (EPIQ 7; Philips Healthcare, Andover, Massachusetts, USA). The American Society of Echocardiography standards were used for all measurements. LV ejection fraction (LVEF) calculation was made by using Biplane Simpson's method [11] (Fig. 2).

Statistical analysis

SPSS 22.0 (Chicago, IL, USA) statistical software package was used to perform all analyses. Whether the distribution of continuous variables is normal or not was evaluated by the Kolmogorov–Smirnov test. In group data, continuous variables were expressed as mean $\pm$ standard deviation. Numbers and percentages were used to specify categorical variables. Categorical variables were compared by the chi-square ($\chi2$) test. Pearson's and Spearman's correlation analysis was used to evaluate the existence of relationship between countable parameters. Serum Elabela levels were statistically significant in the univariate analysis so that multivariate linear regression analysis was performed. Statistically significant *p* value was defined as < 0.05 for all comparisons.

Results

Serum Elabela measurement was successfully obtained from all participants included in the study. The study population was divided into two groups as acromegaly group and healthy control group, and all parameters were compared. When the demographic findings between the acromegaly group and the healthy control group were compared, all parameters except SBP and DBP were found to be similar between the two groups (Table 1). SBP and DBP values were higher in patients with acromegaly. Considering laboratory data, serum glucose, HS-CRP, NT-proBNP, Insulin-like growth factor 1, GH and serum Elabela levels were higher in patients with acromegaly. All other laboratory

Fig. 2 Scatter plot diagram of the relationship between serum Elabela levels and left ventricular ejection fraction

parameters were similar across groups (Table 1) . It was found that LVEF was lower in patients with acromegaly than in the healthy control group (Table 1). Correlation analysis was performed between serum Elabela and other demographic, clinical, laboratory and echocardiographic parameters (Table 2). Linear regression analysis was performed for the parameters that were significantly associated with serum Elabela in the univariate analysis. As a result of this analysis; SBP, NT-proBNP, IGF-1, and GH values were found to be closely and positively related to serum Elabela level, whereas age and LVEF values were found to be closely and negatively related (Table 2).

Discussion

The most important finding of our study is that serum Elabela level was found to be significantly increased in patients with acromegaly compared to healthy controls. As far as we know, our study is the first study to show that serum Elabela levels are increased in patients with acromegaly. Another important finding of our study is determining that serum Elabela level in acromegaly patients is closely related to low LVEF and high NT-proBNP serum levels, which are among the findings of cardiovascular involvement. Many parameters have been investigated in the studies on the effects of apelin and Elabela on the cardiovascular system, and the findings show that they slow down the course of diseases that cause cardiac hypertrophic and fibrotic processes such as hypertension, heart failure, and MI [10]. Due to all these positive and cardiovascular protective effects, it was thought that they could be targets for possible treatment methods [12]. Although there are many studies on cardiovascular diseases and their relation to serum Elabela or Apelin level [7, 8], as far as we have investigated, there is no study on serum Apelin or Elabela level in patients with acromegaly. As it is known, HT is very common in acromegaly patients and is associated with left ventricular hypertrophy [2, 3. 13.]. Also, increased GH and IGF-1 levels in acromegaly patients are associated with decreased systolic functions in these patients [3, 13]. These peptides (Apelin and Elabela), which are generally cardiac protectors and whose synthesis is increased for secondary protection in various cardiovascular diseases, may also have protective effects in patients with acromegaly. In our study, it was found for the first time that serum Elabela level increases significantly in acromegaly patients and is very closely and negatively related to LV-EF and very closely and positively related to NT-proBNP level (Fig. 3). In the light of this important finding obtained in our study, serum Elabela level was thought to increase with the direct activation of the apelin-ergic system in response to the cardiac involvement findings in acromegaly patients. It was thought that the rise in level of Elabela, which increased significantly (approximately tenfold)
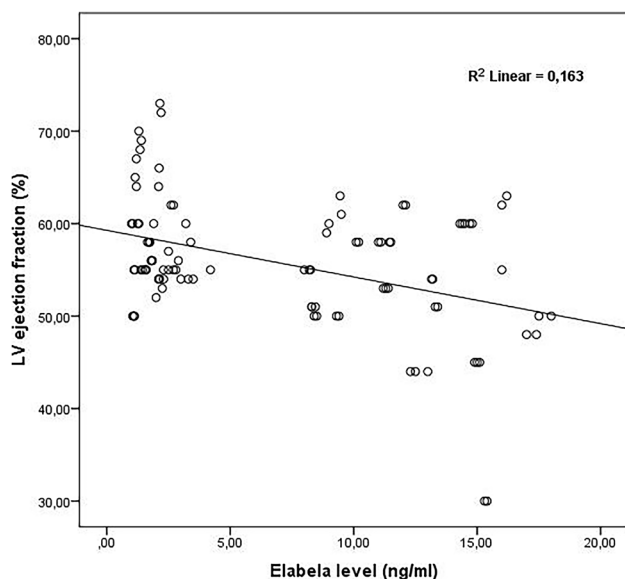
Table 1 Demographic, clinical and laboratory findings of acromegaly patients and healthy controls

Variable	Acromegaly patients (n = 30)	Healthy controls (n = 50)	p
Age (year)	45.1 ± 6.7	44.5 ± 5.3	0.698
Gender (female)	19	17	0.835
Hypertension, n (%)	15 (30%)	-	0.325
Diabetes mellitus, n (%)	16 (32%)	-	0.325
Current smoker, n (%)	21(42%)	-	0.369
Hyperlipidemia, n (%)	7 (14%)	-	0.060
Systolic blood pressure (mmHg)	130 ± 20	110 ± 7.2	**< 0.001**
Diastolic blood pressure (mmHg)	83 ± 15	71 ± 6.1	**< 0.001**
Basal heart rate (pulse/min)	81 ± 11	77 ± 10	0.266
Body mass index (kg/m^2)	28.1 ± 2.4	27.6 ± 1.6	0.164
White blood cell (μL)	7.3 ± 1.9	7.5 ± 1.6	0.855
Hemoglobin (%)	13.1 ± 1.8	12.9 ± 1.2	0.420
Fasting plasma glucose (mg/dL)	109 ± 23	92 ± 5.7	**< 0.001**
Blood urea nitrogen (mg/dL)	33.3 ± 17.8	29.5 ± 4.1	0.140
Creatinine (mg/dL)	0.75 ± 0.49	0.64 ± 0.18	0.131
Total cholesterol (mg/dL)	197 ± 59	180 ± 45	0.435
LDL cholesterol (mg/dL)	135 ± 45	125 ± 22	0.338
HDL cholesterol (mg/dL)	44 ± 15	45 ± 8.2	0.568
Triglyceride (mg/dL)	155 ± 76	140 ± 65	0.244
Hs-CRP (mg/L)	1.69 ± 2.36	0.43 ± 0.31	**< 0.001**
NT-proBNP (pg/mL)	820 ± 685	74 ± 6.7	**< 0.001**
Insulin-like growth factor 1 (ng/dL)	376 ± 182	72 ± 7.6	**< 0.001**
Growth hormone (ng/mL)	9.16 ± 14	1.02 ± 0.52	**< 0.001**
LV ejection fraction (%)	53.3 ± 7.4	58.9 ± 5.4	**< 0.001**
Elabela (ng/mL)	12.4 ± 2.98	1.85 ± 0.59	**< 0.001**

HDL, high density lipoprotein; *LDL*, low density lipoprotein; *Hs-CRP*, High sensitive C reactive protein; *NT-proBNP*, N-terminal brain natriuretic peptide

in patients with acromegaly, may have been due to system activation for cardiovascular protection, similar to previous Apelin and Elabela studies. Since there is no similar study in the literature, the data in our study could not be compared with other studies. Another important result obtained in our study is to show that GH and IGF-1 levels, which are closely related with disease activity in acromegaly patients, are also closely related to serum Elabela level. In this case, the increased activity of apelinergic system may have an effect on slowing or regressing the negative cardiovascular effects of increased IGF-1 levels.

Limitations

Although biochemical measurement of serum Elabela level was performed in our study, no study on APJ receptor level was performed on the tissue samples. It could have been more meaningful to observe similar findings at the cardiac myocytes. In our study, there was a relationship between Elabela level, NT-proBNP level, and LV-EF; however, LV wall thickness and LV mass index measurements were not performed as echocardiographic parameters. If LVH was also evaluated, more meaningful results could be obtained. In our study, the level of Elabela was measured only before acromegaly treatment. Elabela level may have increased with the purpose of cardiac protection such as preventing cardiac hypertrophy and heart failure. Therefore, if the serum level was evaluated after acromegaly treatment, more meaningful results could be obtained. Our study should be supported by new studies with the same characteristics and which evaluates the presence of LVH, examines tissue samples, and measures Elabela level after acromegaly treatment.

Table 2 The parameters associated with serum Elabela level and linear regression analysis for parameters significantly correlated with serum Elabela

	Univariate analyses		Multivariate analyses	
	p	**r**	**p**	**β**
Age (year)	**0.042**	−0.204	**0.002**	−0.100
Systolic blood pressure (mmHg)	**< 0.001**	0.515	**0.001**	0.113
Diastolic blood pressure (mmHg)	**< 0.001**	0.452	0.127	0.089
Basal heart rate (pulse/min)	**< 0.001**	0.618	0.055	0.65
Body mass index (kg/m^2)	**0.021**	0.230	0.267	0.032
Fasting plasma glucose (mg/dL)	**< 0.001**	0.561	0.223	0.043
Blood urea nitrogen (mg/dL)	**0.009**	0.261	0.455	0.021
Creatinine (mg/dL)	**0.010**	0.255	0.372	0.026
Hs-CRP (mg/L)	**< 0.001**	0.411	0.787	0.009
NT-proBNP (pg/mL)	**< 0.001**	0.630	**< 0.001**	0.195
LV ejection fraction (%)	**< 0.001**	−0.433	0.592	0.017
Insulin-like growth factor 1 (ng/dL)	**< 0.001**	0.945	**< 0.001**	0.838
Growth hormone (ng/mL)	**< 0.001**	0.469	**0.002**	0.105

Hs-CRP, High sensitive C reactive protein; *NT-proBNP*, N-terminal brain natriuretic peptide; *LV*, Left ventricle

$R^2_{Adjusted} = 0.936$ in multivariate analyses
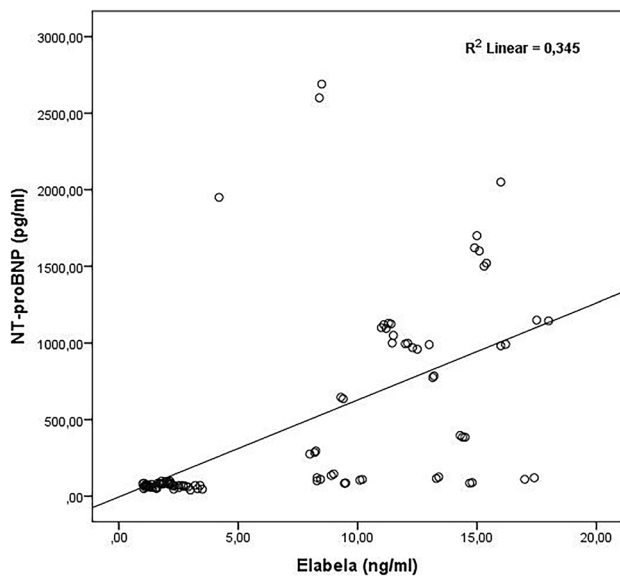
Fig. 3 Scatter plot diagram of the relationship between serum Elabela levels and NT-proBNP

Conclusion

According to the results of our study, patients with acromegaly have increased serum Elabela values compared to healthy controls. This finding could be due to an upregulation of the apelinergic system in order to exert cardiovascular positive effects in response to cardiovascular involvement in patients with acromegaly. High serum Elabela level may be a sign of cardiac involvement in patients with acromegaly. Therefore, Elabela level can also be used as a follow-up parameter in these patients. Patients with high serum Elabela level can be called for frequent follow-ups and examined closely in order to avoid cardiovascular events that may develop in the future. However, this finding still needs to be confirmed by further studies with more participants.

Declarations

Ethics approval and consent to participate The study was performed according to the recommendations set by the Declaration of Helsinki on Medical Research involving Human Subjects. The ethics committee of Cukurova University, Faculty of Medicine approved the study. Informed consent was obtained from all individual participants included in the study.

Conflict of interest The authors declare no competing interests.

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