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ORIGINAL RESEARCH

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The relationship between serum adropin levels and erectile dysfunction

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Abstract

Erectile dysfunction (ED) is associated with endothelial damage, especially atherosclerosis. The search for biomarkers that can predict ED still continues. Adropin is known to affect nitric oxide (NO) bioavailability and energy homeostasis. In our study, we have aimed to investigate the relationship between serum adropin levels and ED. Male patients with and without ED between 40–60 years of age, who presented to the outpatient clinics of urology between November 2019–February 2020, were prospectively included in the study. Biochemical values measured at the time of admission to the outpatient clinic. According to the International Index of Erectile Function-5 (IIEF-5) scores which range between 5 and 25 points, patients with a score $\leq$21 were considered to have ED. The patients were divided into two groups: as ED and non-ED control groups. Laboratory values obtained at admission to outpatient clinics of urology were compared between groups. Patients with (n: 40), and without (n: 40) ED were included in the study. The mean age (50.2 $\pm$ 5.7 years), average body mass index (BMI) (29.7 $\pm$ 2.5 kg/m^2), IIEF score (15.8 $\pm$ 6 pts), serum adropin (584.8 $\pm$ 172 pg/mL), and total testosterone (396.4 $\pm$ 91.7 ng/dL) levels were recorded. Serum adropin and testosterone levels were statistically significantly higher in the non-ED group than in the ED group (712.3 $\pm$ 222 pg/mL *vs.* 511.1 $\pm$ 145 pg/mL, $p < 0.001$ and 420.5 $\pm$ 56 ng/dL *vs.* 374.3 $\pm$ 98 ng/dL, respectively $p = 0.032$). Whereas fasting blood glucose (FBG) values were found to be statistically significantly higher in the ED group (100.2 $\pm$ 14 mg/dL *vs.* 143.8 $\pm$ 78 mg/dL, $p = 0.001$). According to the results of our study, serum levels of adropin which improves endothelial functions were comparatively lower in ED patients, as expected.

Keywords

Adropin; Biomarkers; Erectile dysfunction; Total testosterone

1. Introduction

Erectile dysfunction is defined as the inability to achieve or maintain an erection sufficient for satisfactory sexual intercourse [1]. ED has a complex multifactorial mechanism that includes disruption of neural, vascular and hormonal signaling pathways. Organic causes of ED are associated with vascular risk factors. In current guidelines, total testosterone levels, fasting blood glucose, lipid profile are assessed in the initial diagnostic evaluation of ED [1].

The presence of ED is thought to be a marker for cardiovascular diseases. Vasculogenic ED, in particular, is thought to carry an independent risk for future cardiovascular events [2, 3]. European Association of Urology (AUA) Guidelines suggest the use of risk stratification algorithm developed by The Second Princeton Consensus on Sexual Dysfunction and Cardiac Risk to determine the cardiac risk of ED patients. However, the use of biomarkers may be more useful for younger patients who are not included in this risk classification group. Therefore, it is vital to specify biomarkers that can help identify patients at higher cardiovascular risk and also predict cardiovascular events.

In recent years, potential biomarkers of atherosclerosis and cardiovascular diseases have been started to be used [4, 5]. One of these molecules is adropin, a peptide consisting of 76 amino acids. Adropin has been shown to be first synthesized in the liver and its production is encoded by the Energy Homeostasis Associated gene (*Enho* gene) [6]. Adropin is known to be associated with insulin sensitivity, energy balance and lipid metabolism [7]. There is a relationship between endothelial dysfunction and low adropin levels. Some studies in the literature have shown the presence of strong relationships between low adropin levels and cardiovascular events [8, 9]. From a pathophysiological perspective, vasculogenic ED may result from endothelium-dependent or independent impairment of smooth muscle relaxation, occlusion of penile arteries, or a combination of these.

Despite the ongoing researches to determine potential biomarkers reflecting the severity of erectile dysfunction, an ideal biomarker that will predict ED has not yet been found.

In our study, we have aimed to investigate whether serum adropin levels could be used as a potential biomarker in ED that shares a common pathophysiology with cardiovascular diseases.

2. Materials and methods

Patients with ED aged 40–60 years who presented to the urology outpatient clinic between November 2019–February 2020 were prospectively included in the study. Age, comorbidity and body mass index (BMI) values of the patients were recorded. Serum prostate specific antigen (PSA), FBG, creatinine, tiroid stimulating hormone (TSH), thyroxine (T4), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transferase (GGT), total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), triglyceride, C reactive protein (CRP), total testosterone and serum adropin levels, and sedimentation rates of the patients were recorded at the time of admission to the outpatient clinic. Blood samples were taken from all participants at 08:00 in the morning after a 12-hour fast and stored at −20 °C. Total testosterone, fasting levels of blood glucose, triglyceride, LDL, HDL and serum adropin levels were measured.

Adropin levels were measured by using an adropin (ENHO) Enzyme-Linked Immunosorbent Assay (ELISA) reagent kit (03260502, USCN Life Science Inc, Wuhan, China). The analytical (linear) detection range for adropin was 31.2–2000 pg/mL for adropin. The minimal detection limit was 12.9 pg/mL.

The onset time of the patients' ED was recorded, and ED patients were asked to fill out the IIEF-5 form reflecting their erectile function status in the previous month. According to total IIEF-5 scores (5–25), patients with ED were divided into severe (5–7), moderate (8–11), mild-moderate (12–16) and mild (17–21 ED) groups. Patients with IIEF-5 score <21 were considered to have ED.

Patients who received any treatment that could affect ED (hormone replacement therapy, GnRH agonist), who had a history of smoking, alcohol or substance use, psychiatric disease, cancer, neurological disorders, acute/chronic urinary tract inflammation, end-stage renal failure and penile surgery were excluded from the study.

Male patients of the same age group who presented to the urology outpatient clinic with flank pain without ED symptoms were included as the control group. Biochemical parameters measured in peripheral blood and serum adropin levels were compared between both groups.

3. Statistical analysis

Statistical analysis was performed with IBM SPSS V21 (IBM Corp., Armonk, NY, USA). The normality of the distribution was examined by the Kolmogorov-Smirnov test. Continuous variables were expressed as means ± standard deviations (SD), minimum–maximum values and compared with Student's *t*-test. Categorical variables were reported as numbers (percentages). Pearson's correlation analysis was used to assess the relationship of the parameters with ED. The Receiver Operating Characterictic (ROC) curve analysis was used to examine the role of adropin in the differentiation of ED. Logistic regression analysis was utilized to identify risk factors and predictors for ED. The G-Power 3.1.9.4 (University of Düsseldorf, Düsseldorf, Germany) statistical power analysis program was performed to calculate the sample size of the study. A two-tailed $p < 0.05$ was considered statistically significant.

4. Results

Based on the results of the power analysis (two-way correlation, type-1 error rate (α) = 0.05, power of the study ($1 - \beta$) = 0.80, and effect size = 0.52), an adequate number of patients were included in each group (ED group n: 40, control group n: 40). The mean age (50.2 ± 5.7 years), average BMI (29.7 ± 2.5 kg/m^2), IIEF score (15.8 ± 6 pts), serum adropin (584.8 ± 172 pg/mL), and total testosterone (396.4 ± 91.7 ng/dL) levels were also recorded.

No difference was found between the groups with and without ED in terms of the incidence of coronary artery disease (CAD), diabetes mellitus (DM) and hypertension (HT) (Table 1). No statistically significant difference was found between the two groups in terms of age, BMI, serum PSA, creatinine, TSH, AST, ALT, GGT, total cholesterol, HDL, LDL, triglyceride, CRP values, and sedimentation rates. The average IIEF-5 score of the non-ED group (23.63 pts) was statistically significantly higher that that of the ED group (13.1 pts) ($p < 0.001$). Serum adropin, and testosterone levels were statistically significantly higher in the non-ED group relative to the ED group (712.3 ± 222 pg/mL *vs.* 511.1 ± 145 pg/mL, $p < 0.001$ and 420.5 ± 56 ng/dL *vs.* 374.3 ± 98 ng/dL, $p = 0.032$). While FBG values were statistically significantly higher in the ED group (100.2 ± 14 mg/dL *vs.* 143.8 ± 78 mg/dL, $p = 0.001$) (Table 2).

Whereas, a moderately positive significant correlation was detected between serum adropin levels and IIEF-5 scores ($p < 0.001$; correlation coefficient: +0.544) (Fig. 1).

According to the results of univariate logistic regression analysis, only serum adropin levels were found to be an independent predictor for ED (Odds ratio (OR): 0.993 95% confidence interval (CI): 0.988–0.997, *p*: 0.001).

The sensitivity, and specificity of accepted cut-off value of serum adropin (719.5 pg/mL) in the prediction of ED were determined as 0.975 and 0.450, respectively Area under curve (AUC): 0.789 (95% CI: 0.692–0.885, $p < 0.001$) (Fig. 2).

5. Discussion

Erectile dysfunction and atherosclerosis have many common risk factors, including disorders of lipid metabolism, endothelial dysfunction and vascular inflammation. Vascular endothelial cells produce molecules such as nitric oxide and endothelin, which act as a barrier between the blood and the blood vessel wall. Many factors, especially inflammatory factors, cause endothelial damage. Low serum adropin levels have been associated with endothelial dysfunction and progression of atherosclerotic process [10]. In our study, we investigated whether adropin levels in ED patients differ from those of the healthy population. According to our results, serum adropin

TABLE 1. Comparative analysis between ED, and non-ED groups in terms of comorbid diseases.

Variables	Non-ED group n: 40	ED group n: 40	*p* value
DM, n (%)			
Absence	33 (82.5%)	32 (80%)	0.775
Presence	7 (17.5%)	8 (20%)	
HT, n (%)			
Absence	34 (85%)	33 (82.5%)	0.762
Presence	6 (15%)	7 (17.5%)	
CAD, n (%)			
Absence	37 (92.5%)	36 (90%)	0.692
Presence	3 (7.5%)	4 (10%)	

ED: Erectile dysfunction; CAD: Coronary artery disease; DM: Diabetes mellitus; HT: Hypertension.

TABLE 2. Comparative analysis of biochemical parameters, and demographic characteristics between ED, and non-ED groups.

Variables	Non-ED group n: 40	ED group n: 40	*p* value
Age (yr) (mean ± SD)	48.9 ± 7.9	51.1 ± 9.4	0.257
Height (cm) (mean ± SD)	172.9 ± 6.3	172.0 ± 6.5	0.536
Body weight (kg) (mean ± SD)	81.7 ± 11.1	83.4 ± 13.7	0.563
BMI (kg/m^2) (mean ± SD)	27.3 ± 3.2	28.1 ± 4.2	0.324
Total testosterone (ng/dL) (mean ± SD)	420.5 ± 56.8	374.3 ± 98.0	0.032
PSA (ng/mL) (mean ± SD)	1 ± 0.7	1 ± 0.8	0.895
FBG (mg/dL) (mean ± SD)	100.2 ± 14.5	143.8 ± 78.2	0.001
Creatinine (mg/dL) (mean ± SD)	0.9 ± 0.1	0.9 ± 0.1	0.532
TSH (mU/L) (mean ± SD)	1.6 ± 1.0	2.7 ± 7.2	0.359
T4 (μg/dL) (mean ± SD)	1.1 ± 0.1	1.2 ± 0.4	0.226
AST (U/L) (mean ± SD)	29.1 ± 8.4	27.6 ± 10.0	0.464
ALT (U/L) (mean ± SD)	37.1 ± 19.4	31.9 ± 15.3	0.192
GGT (IU/L) (mean ± SD)	43.4 ± 19.7	43.0 ± 36.6	0.955
Total cholesterol (mg/dL) (mean ± SD)	202.7 ± 33.2	209.6 ± 51.9	0.481
HDL (mg/dL) (mean ± SD)	45.4 ± 8.5	47.3 ± 9.9	0.357
LDL (mg/dL) (mean ± SD)	142.7 ± 31.4	129.7 ± 43.5	0.129
Triglyceride (mg/dL) (mean ± SD)	247.2 ± 96.3	253.5 ± 129.4	0.807
Sedimentation rate (mm/h) (mean ± SD)	5.2 ± 4.3	4.9 ± 2.9	0.698
CRP (mg/dL) (mean ± SD)	3.9 ± 3.4	3.5 ± 2.3	0.486
IIEF-5 score (mean ± SD)	23.63 ± 1.079	13.10 ± 2.700	<0.001
Adropin (pg/mL) (mean ± SD)	712.3 ± 222.7	511.1 ± 145.6	<0.001

ED: Erectile dysfunction; BMI: Body mass index; PSA: Prostate specific antigen; FBG: Fasting blood glucose; TSH: Thyroid stimulating hormone; T4: Thyroxine; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: Gamma glutamyl transferase; HDL: High density lipoprotein; LDL: Low density lipoprotein; CRP: C reactive protein; IIEF: International index of erectile function; SD: standard deviations.

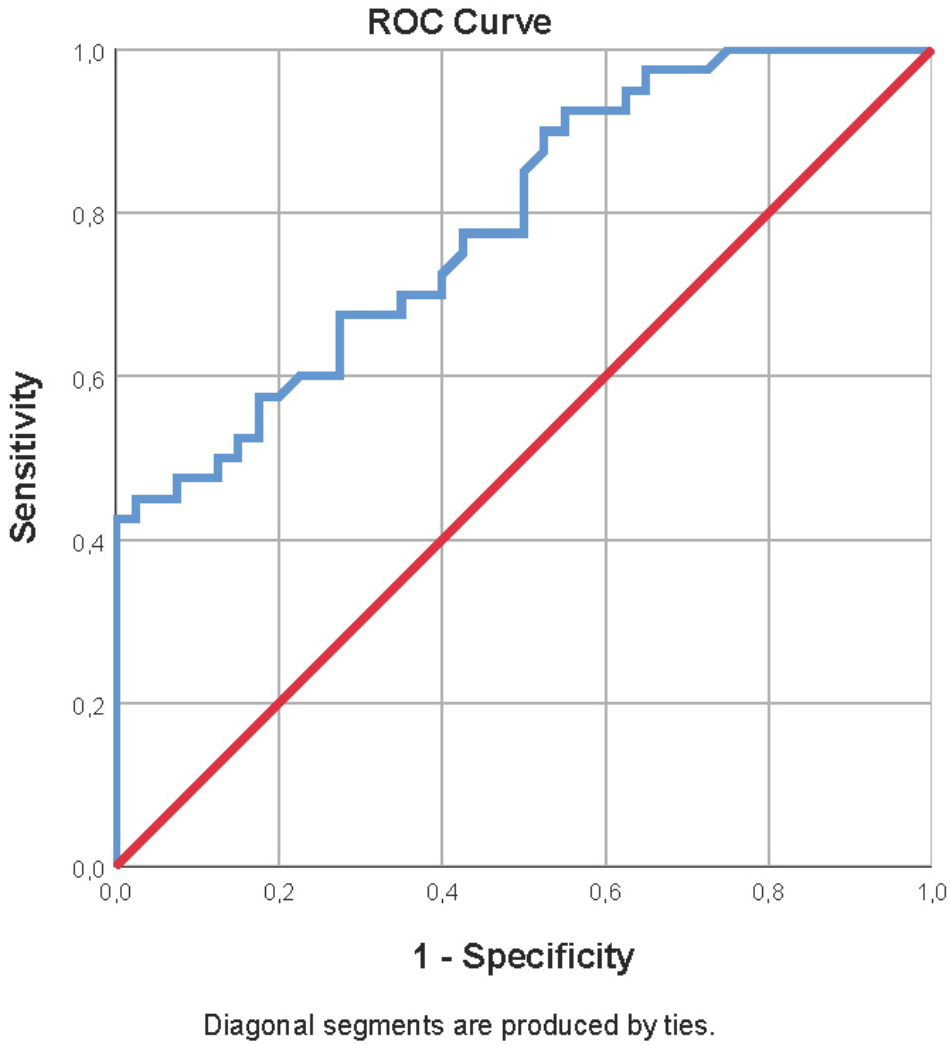

FIGURE 1. ROC analysis of adropin in the prediction of ED. ROC: Receiver operating characteristic.

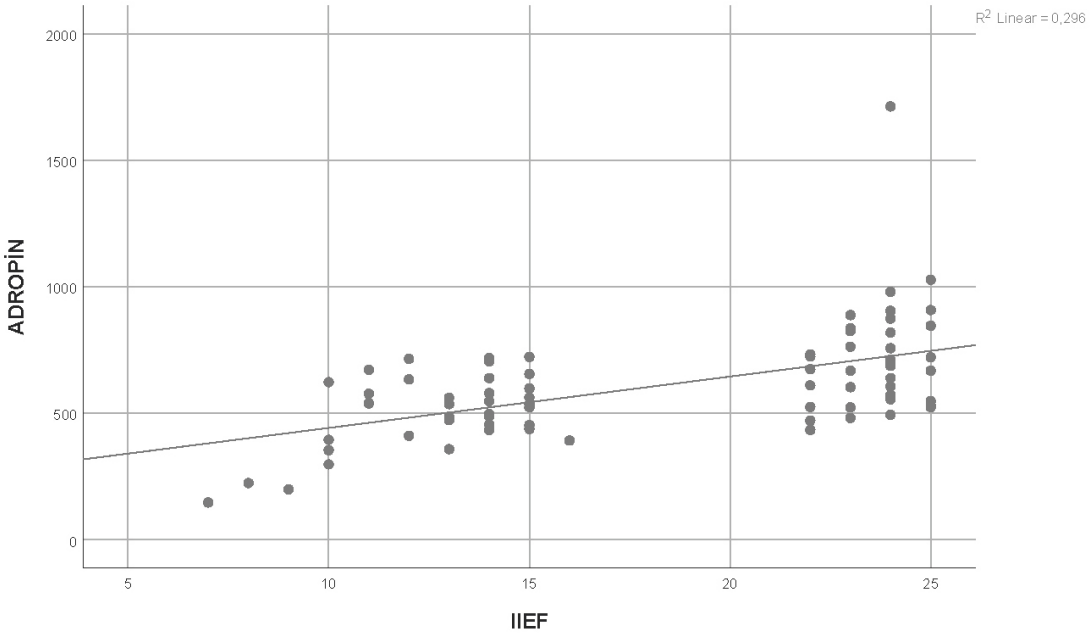

FIGURE 2. Correlation analysis between serum adropin levels and IIEF-5 scores. IIEF: International index of erectile function.

levels in the ED group were significantly lower compared to the control group.

Adropin is a newly identified, stable secretory protein encoded by the *Enho* gene. Adropin secretion occurs in liver, brain, umbilical vein and coronary artery endothelial cells. Low adropin level is a risk factor for cardiovascular diseases [6]. Adropin synthesis occurs mainly in the middle and posterior lobes of the brain. Studies have shown that adropin improves endothelial function, reduces insulin resistance and increases glucose oxidation. In their study on mice, Altamimi *et al.* [11] showed that adropin has a key role in cardiac energy metabolism by increasing glucose oxidation, cardiac insulin signaling and decreasing lipid oxidation. In their study, Yang *et al.* [12] concluded that adropin *Enho* RNA and protein levels in old rats were lower than in young rats. In their systematic review, Yosaee *et al.* [13] showed that serum adropin levels were significantly decreases in patient groups with acute myocardial infarction, atherosclerosis, and cardiac syndrome X compared to the control group.

Organic ED basically develops in the presence of impaired vascular pathogenesis. Due to relatively small diameters of penile artery, ED appears as the first symptom of vascular pathologies. The endothelium is an important part of the vascular microenvironment. As a result of endothelial dysfunction, blood flow to the relevant organ decreases. NO plays a fundamental role in the mechanism of penile erection. In endothelial dysfunction, disruptions in NO pathways occur. Presumably, adropin may have an effect on ED by acting on this pathway. In a study by Celik *et al.* [14], adropin and NO levels decreases in the patient group with higher angiographic scores. In parallel with the results of above-mentioned studies, in our study serum adropin levels were lower in the ED group than in the control group.

The mechanism of action of adropin can be explained in several ways. Adropin possibly enhances the bioavailability of NO by increasing the expression of the NO synthase enzyme. Secondly, adropin directly protects endothelial function from exogenous insults. In their study on mice, Sato *et al.* [15] found that adropin could prevent atherogenetic process independently of glucose, lipid and hypertension. According to the authors, adropin prevents the early vascular inflammatory response through inflammatory signalling pathways driven by non-lipid factors [15]. According to the meta-analysis results of 7 studies involving 945 patients regarding adropin, adropin levels in patients with CAD, acute myocardial infarction, unstable angina pectoris and stable angina pectoris were found to be significantly lower than the control group patients [16].

Testosterone plays a role in all stages of the male sexual cycle and has a key role in the pathogenesis of ED. In our study, we found that the mean total serum testosterone level decreases in the ED group. Obesity is known to be a serious risk factor for ED. In their study, Muhammed *et al.* [17] concluded that testosterone and adropin levels in obese men were found to be lower than in men of normal weight. In their study, the authors stated that adropin may affect the secretion of gonadotropin releasing hormone, and subsequently serum testosterone levels through the hypothalamic pathways [17].

Adropin has been investigated as a biomarker in many diseases with endothelial dysfunction, such as ED. Kutlu *et al.* [18] investigated adropin levels in a group of patients with non-alcoholic fatty liver disease. They concluded that adropin levels in these patients were statistically significantly lower than in the control group. Additionally, adropin levels decreases in the group with higher insulin resistance [18]. Zhang *et al.* [19] investigated the effect of aerobic exercise on serum adropin levels in obese patients. After the 3 months exercise program, serum adropin levels showed a statistically significant increase in the obese group [19]. Brnić *et al.* [20] investigated the role of adropin in inflammatory bowel disease, in which inflammation plays an important role in its pathogenesis. According to the results of the study, which included 55 inflammatory bowel disease patients and 50 healthy subjects, statistically significantly lower serum adropin levels were found in the inflammatory bowel disease group relative to the control group. No difference was found between groups of ulcerative colitis and Crohn's disease in terms of serum adropin levels [20].

The most important limitation of our study is that it was conducted with a small number of patients.

6. Conclusions

The protective effect of adropin on endothelial functions is known. According to the results of our study, serum adropin levels in the healthy group were found to be significantly higher than in the ED group. If our results are supported by studies with a larger number of patients, a guiding role of adropin played in both the diagnosis and treatment of ED patients may be disclosed.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

EK and AE—designed the research study. OE—performed the research. AB and MS—provided help and advice on statistics. MK and CM—analyzed the data. OE, AE and EK—wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was reviewed and approved by the ethics committee of Erzincan Binali Yıldırım University of Erzincan Province, Turkey (no: 10/09 and date: 10 August 2019). Informed consent was obtained from all participants in the study.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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