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The relationship between erectile dysfunction and serum adropin level in male patients with type 2 diabetes mellitus

Gizem Arslan[1], Ali Özdemir[2]

[1]Department of Internal Medicine, İnegöl State Hospital, Bursa, Türkiye
[2]Department of Internal Medicine, University of Health Science Fatih Sultan Mehmet Training and Research Hospital, İstanbul, Türkiye

ABSTRACT

Objectives: Diabetes Mellitus is a chronic, progressive disease with increasing worldwide prevalence and is a public health problem because of the high cost of treatment and complications. Adropin has been discovered in recent years, and it has been reported to be associated with glucose, lipid metabolism, and endothelial dysfunction. In this study, it was aimed to investigate the relationship between erectile dysfunction and Adropin level in Type 2 diabetic male patients.

Methods: Forty patients with type 2 DM with erectile dysfunction and 25 patients with type 2 DM without erectile dysfunction, aged between 40 and 60, who applied to the internal medicine outpatient clinic between November 2019 and March 2020, were included in the prospective study. In addition to routine blood tests in the study groups, Adropin levels were measured using the ELISA method.

Results: The study was conducted with 65 men aged 40 and 60 between November 2019 and February 2020. The mean age of the men was 52.71±6.04. The study used 40 (61.5%) Case groups and 25 (38.5%) Control groups. The case group consisted of 12 (18.5%) Mild ED, 20 (30.8%) Moderate ED, and 8 (12.8%) Severe ED, and the control group consisted of Type 2 Diabetes Mellitus Patients without erectile dysfunction.

Conclusion: According to our results, serum Adropin levels in Mild ED, Moderate ED, and Severe ED groups were found to be higher than those in Type 2 Diabetes Mellitus patients without erectile dysfunction.

Keywords: Diabetes mellitus, Adropin, Erectile Dysfunction

Diabetes mellitus (DM) constitutes a significant health problem. Every year, 8 to 14 million people die worldwide due to diabetes and other chronic diseases such as cardiovascular diseases and cancer. Type 2 diabetes is increasing rapidly in all developed and developing societies. The diabetes epidemic is mentioned in developing countries, especially in communities migrating from these countries to developed countries.[1, 2] The main reasons for this are the increase in obesity and physical inactivity due to population growth, aging, and lifestyle changes brought about by urbanization.[3] Diabetes ranks fifth among the diseases that cause death in many countries.[4,5] DM is the most common cause of end-stage renal disease, blindness under 65 years of age, and non-traumatic among the diseases that cause death in many countries.[4,5]

Adropin was first described in 2008 by Kumar *et al*. It is a peptide hormone discovered by.[6] It is coded over the gene related to energy balance (ENHO), and it is produced by the liver and brain tissue in the first studies.[7] It has an approximate molecular weight of

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Address for correspondence: *Gizem Arslan. Department of Internal Medicine, İnegöl State Hospital, Bursa, Türkiye*
E-mail: gizem_kgol@hotmail.com

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7,927 kDa and comprises 76 amino acids. The release of Adropin in the body is regulated by hunger and nutrition.

Erectile dysfunction (ED) is defined as the inability to achieve and/or maintain an erection adequate for sexual activity.[8,9] ED has profound effects on psychosocial health and negatively affects patients' quality of life.[10,11] Penile erection is a complex psycho-neurovascular event characterized by increased arterial flow, relaxation of sinusoidal smooth muscles, and decreased venous return, resulting from the coordinated work of neuromediators, striated and smooth muscles, and tunica albuginea.[12] Increasing knowledge about ED increases the number of patients seeking treatment and searching for reliable, appropriate, and well-tolerated treatment.[13]

ED is a severe medical problem that affects more than 100 million men and their sexual partners worldwide. According to an optimistic estimate, the worldwide incidence is around 20 million men.[14]

In this study, we aim to determine the relationship between blood serum Adropin levels in male patients diagnosed with Type 2 DM, according to the presence of erectile dysfunction, between the patient groups and the control group.

METHODS

The Istanbul Fatih Sultan Mehmet Training and Research Hospital local ethical committee approved the study with the decision dated 02.08.2013 and numbered 0208. Forty patients with Type 2 DM with erectile dysfunction and 25 patients with Type 2 DM without erectile dysfunction, aged between 40 and 60 years, who applied to the Diabetes Polyclinic of Fatih Sultan Mehmet Training and Research Hospital between November 2019 and March 2020 were included in the study. The patients who agreed to participate in the study were informed, and a consent form was issued. Stories of all participants included in the study were taken, and systemic physical examinations were performed. The drugs the patients were taking were determined in the patient groups. BMI [BMI=Weight (kg)/Height $(m)^2$] of all participants was calculated. Individuals with atherosclerotic heart disease, kidney failure, smoking, urological evaluation of erectile dysfunction other than diabetes, diabetes for less than 1 year, and chronic diseases other than hyperlipidemia were not included in the study.

The name, surname, age, gender, date of diagnosis, waist circumference, medications used, and examination results of the patients included in the study were recorded in the study forms for analysis. Other clinical features and biochemical parameters of the patient groups (HbA1c, total cholesterol,

HDL-cholesterol, LDL-cholesterol, triglyceride), and drug treatments, if any, were recorded from the patient files simultaneously during their routine application and evaluated.

After 8-10 hours of fasting, 5 ml blood samples were taken from the antecubital vein to study the Adropin levels from the study groups. A straight biochemistry tube was used for blood samples. After the blood was taken into the biochemistry tube and was kept for 45 minutes, it was centrifuged at 3500- 4000 rpm for 5 minutes, and the serum was separated. The separated serums were stored in 2 ml Eppendorf tubes in a deep freezer at -80°C to study Adropin levels.

After the serums were brought to room temperature and melted on the working day, serum Adropin levels were studied with the appropriate ELISA kit (Bioassey technology laboratory catalog no: E3231Hu, Shanghai, China) following the working method in Fatih Sultan Mehmet Training and Research Hospital Biochemistry Department Laboratory.

Statistical Analysis

While evaluating the findings obtained in the study, the IBM SPSS Statistics 22.00 (IBM SPSS, Turkey) program was used for statistical analysis. While considering the study data, the conformity of the parameters to the normal distribution was evaluated with the Shapiro-Wilks test. While considering the study data, the One-way ANOVA test was used to compare normally distributed parameters in contrast to quantitative data and descriptive statistical methods (mean, standard deviation, frequency). The Kruskal-Wallis test was used to compare the parameters that did not show normal distribution, and Dunn's test was used to determine the group that caused the difference. Mann-Whitney U test was used to compare two parameters that did not show normal distribution. Fisher Freeman Halton test was used to compare qualitative data. Pearson correlation analysis was used to analyze the relationships between parameters conforming to the normal distribution. Spearman's rho correlation analysis examined the relationships between parameters that did not conform to the normal distribution. Significance was evaluated at the $p<0.05$ level

RESULTS

The study used 40 (61.5%) Case groups and 25 (38.5%) Control groups. The case group consisted of 12 (18.5%) Mild ED, 20 (30.8%) Moderate ED, and 8 (12.8%) Severe ED, and the control group consisted of Type 2 Diabetes Mellitus Patients without erectile dysfunction. The age of diabetes is below 10 years in 67,7 % of the cases and over 10 years in 32.3% of the cases. While 64.6% have hyperlipidemia, 35.4% do not. Statins are used in 36.9% and not used in 63.1%. While 95.4% use oral antidiabetics, 4.6% do not use it. While insulin is used at 38.5%, it is not at 61.5%. While ASA is used in 21.5%, it is not in 78.5%. Erectile dysfunction is mild in 30%, moderate in 50% and severe in 20%.

There was no statistically significant difference between the case and control groups in terms of age, BMI, diabetes age, waist circumference, HbA1c, total cholesterol, HDL, LDL, and triglyceride parameter values, statin use rates, oral antidiabetic use rates, insulin use rates and Acetylsalicylic acid (ASA) use rates (p>0.05) (Table 1).

The serum Adropin level values of the case group were statistically significantly higher than the Type 2 Diabetes Mellitus Patients without erectile dysfunction group (p:0.001; p<0.05, Table 2).

There was a statistically significant difference between the groups regarding serum Adropin level values (p:0.008; p<0.05). As a result of the pairwise comparisons made to determine the difference, The serum Adropin level values of the control group were found to be statistically significantly lower than those of the mild ED and moderate ED groups (p1:0.004; p2:0.006; p<0.05). There was no statistically significant difference between the other groups regarding serum Adropin level values (p>0.05, Table 3).

There was no statistically significant difference in serum Adropin levels between the diabetic age groups and between those with and without hyperlipidemia in the case and Type 2 Diabetes Mellitus Patients without erectile dysfunction groups (p>0.05).

In the mild ED group, moderate ED group, severe ED group, and the Type 2 Diabetes Mellitus Patients

Table 1. Evaluation of study parameters between groups

		Mild ED	Moderate ED	Severe ED	Type 2 Diabetes Mellitus Patients without erectile dysfunction	p
Age		51.75±6.22	52.5±5.72	57.25±2.66	51.88±6.6	**1 0.149**
BMI		28.5±3.97	29.45±4.84	27.88±5.11	27.04±3.4	**1 0.297**
Diabetes Age		8.67±4.33	6.45±3.85	9.5±5.13	8±5.24	**1 0.372**
Waist circumference		103.17±7.25	104.3±10.7	103.25±9.47	98.24±8.54	**1 0.139**
HgA1c(median)		9.21±2.47 (8.8)	7.53±1.37 (7.1)	7.46±1.49 (7)	8.01±1.91 (7.4)	**2 0.192**
Total cholesterol		186.42±35.51	192.55±41.08	157±27.76	186.36±40.15	**1 0.179**
HDL (median)		41.17±10.5 (37.5)	49.5±26.26 (46)	46.25±10.55 (42)	47.08±13.05 (47)	**2 0.579**
LDL		106.5±32.93	109.7±24.22	89±30.4	106.92±28.25	**1 0.363**
Triglyceride		190.5±151 (122.5)	204.05±164.6 (138)	113.13±73.39 (93.5)	159.32±110.71 (109)	**2 0.106**
		n (%)	**n (%)**	**n (%)**	**n (%)**	
Statin use	**Yes**	7 (%58.3)	6 (%30)	2 (%25)	9 (%36)	**3 0.382**
	No	5 (%41.7)	14 (%70)	6 (%75)	16 (%64)	
Oral antidiabetic use	**Yes**	11 (%91.7)	19 (%95)	7 (%87.5)	25 (%100)	**3 0.228**
	No	1 (%8.3)	1 (%5)	1 (%12.5)	0 (%0)	
İnsulin use	**Yes**	7 (%58.3)	5 (%25)	5 (%62.5)	8 (%32)	**3 0.123**
	No	5 (%41.7)	15 (%75)	3 (%37.5)	17 (%68)	
ASA use	**Yes**	3 (%25)	2 (%10)	2 (%25)	7 (%28)	**3 0.485**
	No	9 (%75)	18 (%90)	6 (%75)	18 (%72)	

[1]Oneway Anova Test *[2]Kruskal Wallis Test* *[3]Fisher Freeman Halton Test*

Table 2. Evaluation of serum Adropin level between Case and Control groups

	Serum Adropin level
Case group	167.08±177.5 (82.3)
Control group	131.22±196.38 (57.1)
p	**0.001***

Mann Whitney U Test **p<0.05*

Table 3. Evaluation of serum Adropin level between the groups

	Serum Adropin level
Mild ED	186.04±191.62 (88.7)
Moderate ED	168.25±189.99 (79.1)
Severe ED	135.71±134.62 (79.5)
Type 2 Diabetes Mellitus Patients without erectile dysfunction	131.22±196.38 (57.1)
p	**0.008***

Kruskal Wallis Test **p<0.05*

without erectile dysfunction group, there was no statistically significant relationship between serum Adropin level values and values of age, BMI, diabetes age, waist circumference, HgA1c, total cholesterol, HDL, LDL and triglyceride parameters (p>0.05, Table 4, Figure 1).

The case group has a positive, 34.5%, and statistically significant relationship between serum Adropin level and waist circumference values (p:0.029; p<0.05). No statistically significant relationship exists between serum Adropin level values and BMI, diabetes age, HgA1c, total cholesterol, HDL, LDL, and triglyceride parameters (p>0.05, Table 5, Figure 2).

Type 2 Diabetes Mellitus Patients without erectile dysfunction groups have no statistically significant relationship between serum Adropin level values and age, BMI, diabetes age, waist circumference, HgA1c, total cholesterol, HDL, LDL, and triglyceride parameter values (p>0.05, Table 5, Figure 2).

DISCUSSION

DM is a progressive disease with an increasing prevalence and complications all over the world. The main aim of diabetes is to improve the patient's quality of life and prevent and delay the complications that may develop.

It has been reported that the Adropin molecule, discovered in recent years, is associated with glucose and lipid metabolism. ED is the inability to achieve and/or maintain an erection sufficient for sexual activity.

This study aimed to examine the relationship between erectile dysfunction and Adropin levels in Type 2 diabetic male patients.

Penile erection is a neurovascular event that depends on neural integrity, functional circulatory system, and healthy cavernous tissue. Therefore, endothelial dysfunction causes erectile dysfunction. Atherosclerotic vascular disease is shown as a cause of ED in 40-50% of cases over the age of 50. Diabetic adult ED is associated with autonomic neuropathy and endothelial dysfunction.[15] Unlike other independent ED, diabetic ED begins at an earlier age.

Table 4. Evaluation of the correlation between serum Adropin level and demographic and laboratory values between the groups

	Serum Adropin level							
	Mild ED		Moderate ED		Severe ED		Type 2 Diabetes Mellitus Patients without erectile dysfunction	
	r	p	r	p	r	p	r	p
Age (years)	0.317	0.315	0.038	0.875	0.257	0.539	0.051	0.808
BMI (kg/m2)	-0.134	0.677	0.254	0.280	0.846	0.008	0.007	0.972
Diabetes age (years)	-0.082	0.799	-0.082	0.731	0.199	0.637	-0.205	0.326
Waist circumference(cm)	0.151	0.639	0.375	0.104	0.616	0.104	0.159	0.447
HgA1C⁺	-0.322	0.308	-0.257	0.274	-0.214	0.610	-0.034	0.874
Total cholesterol	0.47	0.123	-0.188	0.428	-0.289	0.488	-0.133	0.526
HDL⁺	0.231	0.471	-0.12	0.615	0.503	0.204	-0.042	0.841
LDL	0.179	0.578	-0.215	0.363	-0.215	0.608	-0.087	0.678
Triglyceride⁺	0.070	0.829	-0.100	0.675	-0.229	0.586	0.016	0.938

Pearson Correlation Analysis *⁺Spearman Rho Correlation Analysis*

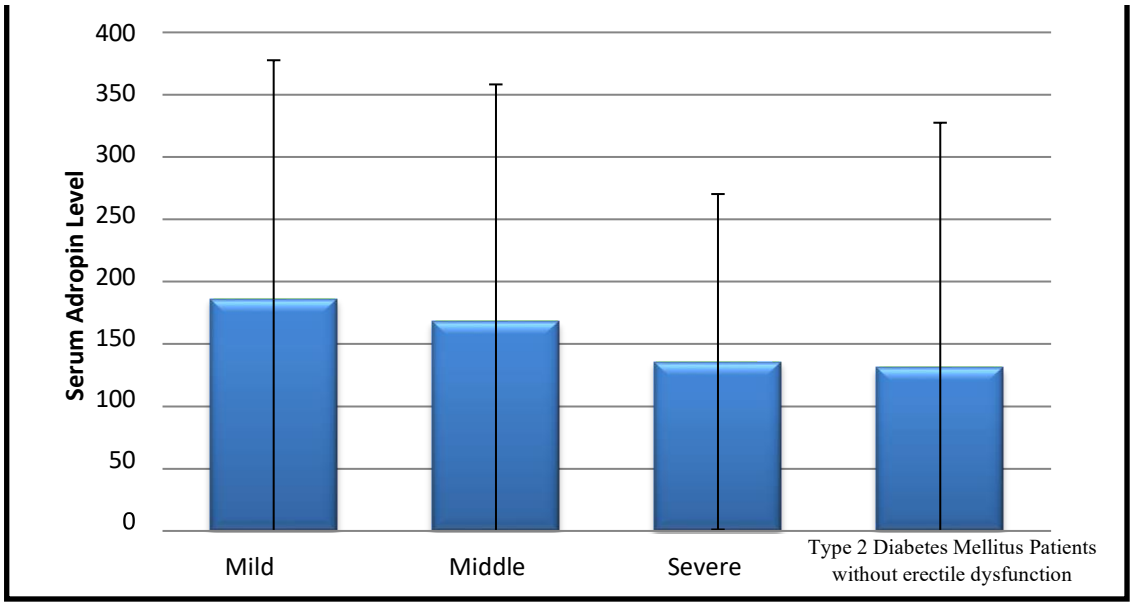

Figure 1. Evaluation of serum Adropin level between groups

This is the second study to determine the relationship between Adropin levels and ED. Adropin participates in Nitric oxide bioavailability and affects inducible nitrite oxide synthase expression. Adropin, encoded by the gene to provide energy homeostasis, is present in various organs such as pancreatic tissue, brain, kidney, endocardium, myocardium, epicardium, and endothelium.[7] Adropin-treated endothelial cells exhibit more significant proliferation, migration, capillary-like tube formation, less permeability, and tumor necrosis factor-α-induced apoptosis.[16]

In their study, Kumar *et al*.[6] showed that blood serum Adropin levels increased in high-fat diets. Another study revealed that excessive secretion of the Adropin hormone or systemic administration of the hormone for treatment in mice with diet-induced obesity decreased insulin resistance and improved glucose tolerance. Celik *et al*.[17], in another study conducted in this area, compared the serum Adropin levels of the patient group diagnosed with gestational DM and the healthy control female group. This study found that the blood serum Adropin level in the patient group with gesta-

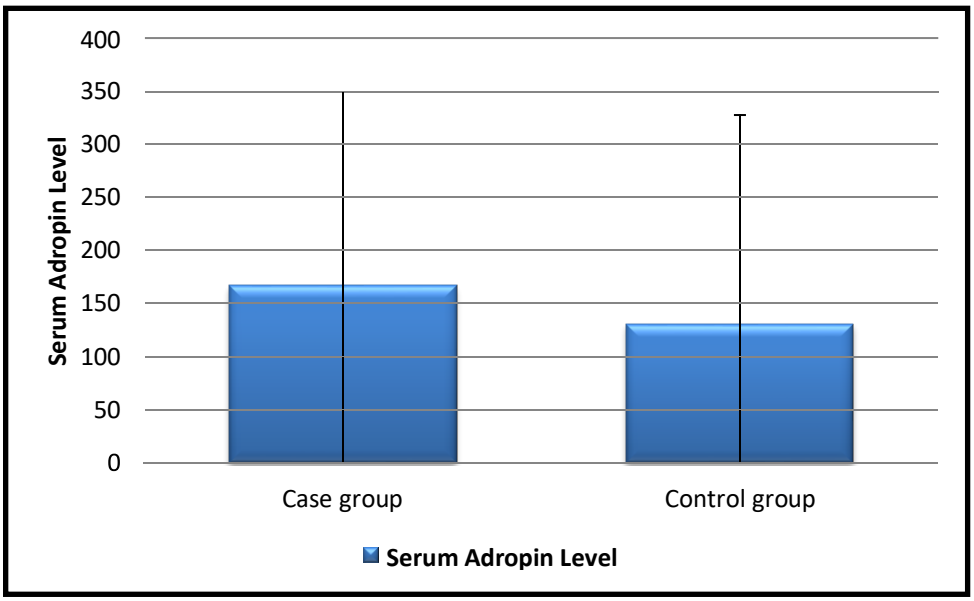

Figure 2. Evaluation of serum Adropin level between Case and Control groups

Table 5. Evaluation of the correlation between serum Adropin level and demographic and laboratory parameters between Case and Control groups

	Serum Adropin level			
	Case group		Control group	
	r	p	r	p
Age (years)	0.107	0.511	0.051	0.808
BMI (kg/m2)	0.239	0.138	0.007	0.972
Diabetes age (years)	-0.04	0.808	-0.205	0.326
Waist circumference (cm)	*0.345*	*0.029**	0.159	0.447
HgA1C⁺	-0.171	0.291	-0.034	0.874
Total cholesterol	0.027	0.867	-0.133	0.526
HDL⁺	0.05	0.759	-0.042	0.841
LDL	-0.041	0.803	-0.087	0.678
Triglyceride	-0.099	0.542	0.016	0.938

Pearson Correlation Analysis *⁺Spearman Rho Correlation Analysis* **p<0.05*

tional DM was statistically significantly lower than in the control group. This result may show us that high Adropin levels may have a role in the development of diabetes. On the other hand, it also suggests that the increase in Adropin levels secondary to high serum glucose levels may be increased to decrease the blood glucose level.

Topuz *et al*. evaluated endothelial dysfunction and flow-mediated dilatation in type 2 diabetes mellitus patients. They found a positive correlation between plasma Adropin levels and flow-mediated dilatation values, and the authors suggested that Adropin levels could be used to quantify endothelial dysfunction.[18]

In a study conducted on cardiac syndrome X (CSX) patients, serum Adropin levels were significantly lower than in healthy subjects. Therefore, it was assumed that lower serum Adropin levels were an independent risk factor for CSX.[26]

Wu *et al*.[19] reported that low serum Adropin levels were associated with coronary atherosclerosis in type 2 diabetic and non-diabetic patients. The authors asserted that lower Adropin levels might be a novel predictor of coronary atherosclerosis.

Celik *et al*.[20], in a study that aimed to determine the relationship between Adropin levels and ED, found that the average Adropin level was significantly lower in patients with ED. Study results show that Adropin levels are higher in the group with severe coronary artery disease, but the difference between the groups is not statistically significant. In light of this information, decreased serum Adropin levels in erectile dysfunction are the expected result.

However, in our study, Type 2 Diabetic patients with serum Adropin levels and erectile dysfunction were found to be significantly higher than those without erectile dysfunction. This is because the circulating pharmacokinetics of Adropin are virtually unknown. Therefore, a single measurement may not be sufficient to evaluate Adropin levels.

To our knowledge, there is no study on serum Adropin levels in patients with diabetic erectile dysfunction. Previously, Palizban *et al*.[21] found that serum Adropin levels were high in the following years as an adaptive response to pathogenic conditions such as endothelial dysfunction, insulin resistance, dyslipidemia, and glucose intolerance in Type 2 DM. Kuloğlu *et al*.[7] reported that high

Adropin levels may play a role in the development of diabetes, and Adropin levels increase secondary to high serum glucose levels to reduce the blood glucose level.

Limitations of the study

The most important limitation is that endothelial dysfunction and the presence of autonomic neuropathy were not tested in our study. A more comprehensive and multicenter study is needed to reveal the role of Adropin in the pathogenesis of ED and its effects on this molecule.

CONCLUSION

This is the first study in the literature investigating Adropin levels in diabetic ED patients. According to our results, serum Adropin levels in Mild ED, Moderate ED, and Severe ED groups were found to be higher than those in Type 2 Diabetes Mellitus patients without erectile dysfunction. If our results are supported by studies with a more significant number of patients,

a guiding role of Adropin may be disclosed in both the diagnosis and treatment of ED patients

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

The Istanbul Fatih Sultan Mehmet Training and Research Hospital local ethical committee approved the study with the decision dated 02.08.2013 and numbered 0208.

Authors' Contribution

Study Conception: GA, AÖ; Study Design: GA; Supervision; GA, AÖ; Funding: GA; Materials: GA; Data Collection and/or Processing: GA; Analysis and/or Data Interpretation: GA; Literature Review: GA; Critical Review: GA; Manuscript preparing: GA.

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