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Clinical Research

The Determination of Serum Adropin Level According to Concentration Levels of HbA1c in Patients with Type 2 Diabetes Mellitus

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Abstract

Purpose: *Adropin is discovered in recent years and it has been reported to be associated with glucose and lipid metabolism . Our aim is to determine the relationship between blood serum adropin levels according to blood glycosylated hemoglobin (HbA1c) concentration values between the patient groups diagnosed with Type 2 Diabetes Mellitus and the control group.*
Methods:*A total of 60 Type 2 DM, 20 prediabetes for observation were recruited from Endocrinology clinic of Fırat University Hospital. In addition, 20 healthy subjects were recruited for comparison as the normal control group. A total of 60 DM patients were divided into 3 equal groups according to HbA1c levels as 20 patients with HbA1c levels greater than 9 %, 20 between 7-9 %, 20 less than 7 %. In addition to routine blood tests, adropin levels were measured by ELISA method.*
Results: *Patients with DM had lower serum adropin levels when compared with the controls (4,12±1,23 ng/mlversus 4,84±1,41 ng/ml, p<0.05). Adropin levels of the group with HbA1c > 9% was lower in comparison with control group (3,23±1,14 ng/ml versus 4,84±1,41ng/ml, p < 0.001). In diabetic patients we determined negative correlation between HbA1c and adropin levels (r=-0.377, p < 0.05).*
Conclusion: *In this study, we found that adropin levels were reduced with increasing levels of HbA1c. It appears that chronic hyperglycemia or poor blood sugar regulation lowers adropin levels. In the future, on this subject further studies are needed*

Keywords*: Cervical length, Early membrane rupture, Preterm premature membrane rupture, Prematurity*

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Introduction

Nowdays, diabetes mellitus (DM) and non-communicable, chronic diseases that share the same risk factors constitute an important health problem. DM is a carbohydrate metabolism disorder characterized by partial or absolute insulin deficiency or insulin resistance in peripheral tissues, leading to many metabolic disorders in the body and hyperglycemia (1). DM brings serious moral and financial responsibilities for both patients and countries. It has been a task for scientists to better understand the pathogenesis of DM disease and to develop new diagnosis, follow-up and treatment models.

Recently, some factors, especially those released from the liver, have been shown to play an important role in systemic metabolism and energy metabolism in nutrition-related situations (2, 3). Adropin is a peptide hormone first discovered by Kumar et al. in 2008 (4). It is encoded over the gene related to energy balance (ENHO), and it has been shown to be produced by the liver and brain tissue in the first studies (4). It has an approximate molecular weight of 7,927 Kda and consists of 76 amino acids. Adropin is a peptide hormone released primarily to participate in the insulin response and maintenance of energy balance. The release of adropin in the body is regulated by hunger and nutrition. It acts on insulin signaling pathways, including reducing glucose production in the liver, and has effects on insulin resistance (3). Adropin is implicated in the resolution of inflammation at the tissue level, acting as an inhibitor of the pro-inflammatory cytokines TNF-α and IL-6. It has been demonstrated that adropin exerts angioprotective effects by enhancing the production of endothelial nitric oxide synthase (5).

In this study, our aim is to determine the relationship between blood serum adropin levels according to blood glycosylated hemoglobin (HbA1c) concentration values between the patient groups diagnosed with Type 2 Diabetes Mellitus and the control group.

Methods

Ethics Committee Approval: Approval for the study was obtained from the Clinical Studies Ethics Committee of Fırat University, Faculty of Medicine, with the decision dated 02.08.2013 and numbered 0208. The adropin kit used in this study was provided by me; No support was received from any institution or organization for this purpose.

Study design: Patients with a diagnosis of Type 2 DM, aged between 30 and 80, who applied to the Fırat University Hospital

Endocrinology outpatient clinic between May 2013 and October 2013 were included in the study. 20 patients with HbA1c level less than 7, 20 patients with HbA1c level between 7 and 9, 20 patients with HbA1c level higher than 9, 20 prediabetic individuals with impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) and twenty healthy control individuals without any disease were recruited. The patients who accepted to participate in the study were informed and a consent document was issued to the patients. Patients with incomplete data were excluded. The demographic characteristics of the patients, laboratory findings were collected from the patient files and electronic records. In the patient groups, the drugs that the patients were taking were determined. The BMIs of all participants [BMI=Weight (kg)/Height (m)^2] were calculated. Individuals with severe heart failure, chronic renal failure, chronic liver disease and acute infectious disease were not included in the study. The name, surname, age, gender, date of diagnosis, 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 (complete blood count, FBG, PBG, HbA1c AST, ALT, urea, creatinine, LDL, HDL, TG), are recorded. Since there was no history of diabetes in the control group, TCS measurement requirement was not sought.

Data collection: 5 ml blood samples were taken from the antecubital vein to study adropin levels after 8-10 hours of fasting for once during their routine application from the study groups. Straight biochemistry tube was used for blood samples. After the blood taken into the biochemistry tube 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 a deep freezer at -80ºC in the Fırat University Hospital Endocrinology clinic in order to study the Adropin levels in 2 mm eppendorf tubes. After the serums are brought to room temperature and thawed on the working day, serum adropin (Phoenix pharmaceutical Inc. catalog no: EK-032-35, lot no: 604526, Burlingame, CA, U.S.A) levels are adjusted in accordance with the working method with the appropriate ELISA kit, Fırat University Faculty of Medicine, Department of Biochemistry. Worked in the Branch Laboratory.

Statistical analysis

The data obtained in the study were shown as mean±standard deviation. SPSS 17.00 computer package statistics program (SPSS Inc. Software, Chicago, USA) was used to prepare the statistics. The normality of the

distribution of the data was evaluated with the Kolmogorov-Smirnov test. Numerical values in the obtained data were compared with One-Way ANOVA, Mann-Whitney U tests and Kruskal-Wallis test, and non-numerical values were compared with chi-square tests. Pearson correlation analysis was used to determine the relationship between the data. Values with $p<0.05$ were considered significant.

Result

The study groups consisted of 60 patients with diabetes, 20 people with prediabetes and 20 healthy control groups. Patients diagnosed with diabetes were divided into 3 groups according to their HbA1c levels, as HbA1c>9, HbA1c 7-9 and HbA1c<7. Age, gender, body mass index (BMI), fasting blood glucose (FBG), postprandial blood glucose (PBG), HbA1c, LDL, HDL, TG levels, routine laboratory data and statistical comparisons of DM, prediabetes and control groups are given in Table 1.

Table 1: Demographic characteristics and routine laboratory data in study groups.

	Control (n=20)	Prediabetes (n=20)	DM(HbA1c<7) (n=20)	DM(HbA1c7-9) (n=20)	DM(HbA1c>9) (n=20)	*P**
Age (year)	48,2±10,6	51,2±8,0	54,5±9,8	56,6±8,1$^{\times\dagger}$	57,4±8,4$^{\times\times\dagger}$	0,021
Female ratio	55.0	65.0	55.0	50.0	55.0	0,914*
BMI (kg/m²)	25,3±2,2	29,0±3,7$^{\times\times\times}$	29,4±4,4$^{\times\times\times}$	28,4±4,7$^{\times}$	28,7±3,1$^{\times\times\times}$	0,002
FBG(mg/dl)	91,8±5,2	111,1±7,2$^{\times\times}$	119,6±28,7$^{\times\times\times}$	151,4±22,8$^{\times\times\times\dagger\dagger}$	220,1±45,1$^{\times\times\times\dagger\dagger}$	<0,001
PBG(mg/dl)		142,4±16,3	161,5±43,3	181,0±37,1†††	281,2±56,6†††	<0,001
HbA1c (%)	4,9±0,4	5,0±0,6	5,9±0,7$^{\times\times\times\dagger\dagger}$	7,8±0,6$^{\times\times\times\dagger\dagger\dagger}$	10,8±1,6$^{\times\times\times\dagger\dagger\dagger}$	<0,001
LDL(mg/dl)	96,4±16,4	116,3±26,1	118,6±36,6	134,9±27,7$^{\times\times\times}$	135,2±54,5$^{\times\times}$	0,002
HDL(mg/dl)	46,6±4,2	46,6±4,2	45,3±5,8$^{\times}$	47,2±6,9	40,0±7,3$^{\times\times\times\dagger\dagger\dagger}$	<0,001
TG(mg/dl)	154,1±26,	152,4±72,5	171,7±79,3	206,4±109,6	204,6±113,4	0,266

DM: Diabetes Mellitus, BMI: Body Mass Index, FFBG: Fasting blood glucose, PBG: Postprandial blood glucose, HbA1c: Hemoglobin A1c.
* Kruskal-Wallis test is the p value. **Chi-square test is the p value.
When Mann-Whitney U test is applied; Compared with the control group; $\times p<0.05$, $\times\times p<0.01$, $\times\times\times p<0.001$. Compared with the prediabetes group; $\dagger p<0.05$, $\dagger\dagger p<0.01$, $\dagger\dagger\dagger p<0.001$.

The mean age was lower in all groups compared to the control group ($p<0.05$). When compared to the control group, BMI was higher in HbA1c>9, HbA1c 7-9, HbA1c<7 and prediabetes groups (for each, respectively; $p<0.001$, $p< 0.05$, $p<0.001$, $p<0.001$). The mean, standard deviation and statistical analysis results of serum adropin levels of the study groups are shown in Table 2.

Table 2. Adropin level of study groups.

	Control (n=20)	Prediabetes (n=20)	DM(HbA1c<7) (n=20)	DM(HbA1c7-9) (n=20)	DM(HbA1c>9) (n=20)	*p**
Adropin(ng/ml)	4,84±1,41	4,68±0,76	4,67±1,04	4,47±0,99	3,23±1,14$^{\times\times\times,\dagger\dagger\dagger}$	<0,001

*Kruskal-Wallis test p value.

When Mann-Whitney U test is applied;

Compared with the control group; × p <0.05, ×× p <0.01, ××× p <0.001.

Compared with the prediabetes group; †p <0.05, ††p <0.01, †††p <0.001

It was observed that the adropine level was the lowest in the group with HbA1c>9 and the highest in the control group.

In the statistical analysis of adropin levels measured in these five groups using the Kruskal-Wallis test, a very strong statistically significant difference was found in terms of adropin levels (p<0.001). In Mann-Whitney U pairwise analyzes performed to determine the source of the statistical difference, a very strong statistically significant difference was found between the group with DM (HbA1c>9) and the control group in terms of serum adropin levels (3.23±1.14, 4.84, respectively). ±1.41 ng/ml) (p<0.001). In addition, when the group with DM (HbA1c>9) and the prediabetes group were compared (3.23±1.14.4.68±0.76 ng/ml, respectively) (p<0.001), and the DM(HbA1c<7) group was compared (respectively, 3.23±1.14, 4.67±1.04 ng/ml) (p<0.001), compared to the group with DM (HbA1c 7-9) (3.23±1.14, 4, respectively) .47±0.99 ng/ml) (p<0.001), there was a very strong statistically significant difference.

Serum adropin levels were measured between the diabetes mellitus group and the prediabetes and control groups. In the statistical analysis of the adropin level measured between the groups using the Kruskal-Wallis test, it was found to be statistically significantly lower in the DM group (p=0.027) (Table 3).

Table 3: Serum adropin level among DM, prediabetes and control groups.

	Control (n=20)	Prediabetes (n=20)	DM (n=60)	*p**
Adropin(ng/ml)	4,84±1,41	4,68±0,76	4,12±1,23	0,027

*Kruskal-Wallis test was applied (p <0.05).

The relationship between the duration of diabetes age and serum adropin level in the group with diabetes mellitus was examined and is shown in Table 4.

Table 4: Serum adropin level according to diabetes age.

	DM age>10 years (n:18)	**DM age<10 years (n:42)**	***p****
Adropin (ng/mL)	3,48±1,13	4,40±1,17	0,014

Adropin level was found to be lower in the group with diabetes age >10 years and there was a statistically significant difference (p=0.014).

Another result of our study was that there was a negative correlation between adropin level and diabetes age in the DM group (r= -0,261, p <0,05), FBG (r= -0,294, p <0,05), PBG (r=-0,276, p <0,05), HbA1c(r= -0,377, p <0,01,respectively).

Discussion

Serum adropin levels were found to be 4,84±1,41ng/mL in healthy controls, 4,68±0,76 ng/mL in the prediabetes group, 4,12±1,23 ng/mL in the DM group (p=0.027). In the DM group with HbA1c>9, adropin level was found to be significantly lower than in the other groups (p<0.001). In our study, we found that as the Hba1c level increased, the adropin level decreased and we found an inverse correlation between them.

The effects of peptides secreted from peripheral organs on insulin sensitivity, lipid and energy metabolisms have been demonstrated. Adropine deficiency has been shown to be associated with increased adipose tissue and insulin resistance. Apart from its metabolic role, most importantly being the suppression of hepatic glucose production and improvement of insulin sensitivity, adropin seems to be an important gatekeeper of vascular health, and thus, an integral component of cardiometabolic diseases. Specifically, the vasoprotective role of adropin is achieved mainly by affecting endothelial NO synthesis (6).In the animal experiment study conducted by Kumar et al. (4), it was shown that the level of adropin hormone decreased in rats formed obese by diet. In the clinical study conducted by Butler et al. (7), adropin level was found to be low in obese patients and there was a negative correlation between adropin and BMI. In addition, Wu et al. (8) and Çelik et al. (9) in their clinical study, serum adropin levels were found to be low in obese patients, but no statistically significant difference was

found. Contrary to these studies, Lian et al. (10) looked at serum adropin levels in heart failure patients. In their study, they found a positive correlation between adropin and BMI. In this study, adropin level was found to be low in obese patients, but there was no statistically significant difference compared to non-obese patients. Another study found an inverse correlation between serum adropin levels and BMI. It was observed that adropin levels decreased as BMI increased (11). In the group of diabetic patients with HbA1c>9, a negative correlation was found between BMI and adropin, and the result we found is similar to the clinical study of Butler et al.

In this study, the highest serum adropin level was detected in the healthy control group and the lowest in the diabetic patient group with HbA1c>9. In the DM group with HbA1c>9, adropin level was found to be significantly lower than the control and prediabetes groups. Also, when we compared the DM patient group with the control and prediabetes groups in terms of serum adropin levels, the serum adropin level was found to be lower in the DM group and it was statistically very significant. In another study conducted by Celik et al. (12), serum adropin levels of 20 patient groups diagnosed with gestational DM and healthy control women were compared. In this study, the blood serum adropin level in the patient group with gestational DM was found to be statistically significantly lower than the control group. In another study, they found that adropin levels in patients with type 2 diabetes mellitus were significantly lower than in healthy individuals (11).

In contrast to these clinical studies, Aydın et al. (13) found higher serum adropin levels in streptozin-induced diabetic mice compared to non-diabetic mice. Although the authors explained why adropin levels were found to be higher in diabetic mice, it was thought that the difference from the clinical studies was probably due to the stress caused by streptozin. Another possibility is that it may have been elevated as a compensatory mechanism as suggested by the authors.

The results of the studies mentioned above and our study results show that adropin levels are low in diabetes. The lack of significant decrease in prediabetes and well-controlled patients suggests that adropin levels decrease as a result of chronic hyperglycemia.

Additionally, low adropin levels have been shown to correlate with a risk of developing diabetic complications such as diabetic retinopathy (14), diabetic nephropathy (15) and gestational diabetes mellitus (16). In another study, they found higher adropin

levels in patients with GDM than in healthy individuals (17, 18). In our study, we found that serum adropin levels were lower in diabetic patients with hypertension and diabetic neuropathy compared to diabetic patients without complications, but it was not statistically significant. In this study, we found that adropin levels decreased as the HbA1c level increased. After the HbA1c level exceeded 9%, there was a dramatic decrease in adropin level and statistically we found a negative correlation between HbA1c level and adropin level. As the HbA1c level increases, the risk of micro and macrovascular complications in diabetes increases. We suggest that low adropin levels may be a risk factor for complications in diabetes, especially endothelial dysfunction. Adropin may be a follow-up criterion to determine the risk of complications in diabetic patients in the long term. It may be a new marker in addition to HbA1c, which shows blood glucose regulation in diabetic patients.

The limitation of the study is that the number of patients was lower in this study compared to the study by Wu et al. Studies with larger patient series can be performed. There was a statistically significant difference between the BMI values of the selected patients and the BMI values of the control group. This may have affected the results. Since the relationship between serum adropin level and HbA1c level was aimed in the planning of this study, the relationship between diabetic complications and adropin could not be fully demonstrated in this study due to the limited number of diabetic patients with complications, and studies with larger series of patients with diabetic complications can be performed.

Conclusion

Diabetes is a condition that causes many diseases and whose etiology has not been fully elucidated. HbA1c levels are utilized in long-term follow-up. In this study, we found that adropin levels decreased as HbA1c levels increased. It is understood that chronic hyperglycemia or poor regulation decreases adropin levels. This suggests that there may be a relationship between adropin levels and complications of DM. Further and larger studies on this subject are needed.

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Author Contributions: Concept: F.A,S.A. Literature Review: F.A Design : F.A,

K.U,S.A Data acquisition: F.AF Analysis and interpretation: F.A,S.A Writing manuscript: F.A Critical revision of manuscript: F.A,S.A

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