Journal of Biology and Today's World
ISSN 2322-3308
Journal home page: http://journals.lexispublisher.com/jbtw

Received: 18 February 2016 • Accepted: 28 March 2016

Research

doi:10.15412/J.JBTW.01050301

Elevated Serum Levels of Adropin in Patients with Type 2 Diabetes Mellitus and its Association with Insulin Resistance

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ABSTRACT

Evidence suggests a hormone peptide named adropin, is involved in lipid metabolism, insulin resistance, and obesity. However, its role in pathogenesis of type 2 diabetes mellitus (T2DM) is still unclear in humans. Therefore, we investigated whether adropin levels are altered in T2DM patients, and evaluated its association with diabetes- related parameters. Men with T2DM (n=40) and age-matched healthy men (n=40) were participated in case-control study. Serum adropin levels were determined by ELISA. Adropin levels were found to be significantly (p=0.004) higher in T2DM patients (median=2.5ng/ml; interquartile range=1.28ng/ml) compared to healthy controls (Median=1.9ng/ml; interquartile range =0.6ng/ml). Adropin was inversely correlated with FBG (Spearman's rho= -0.335; *p*=0.017) in T2DM patients and was also negatively correlated with HOMA-IR (Spearman's rho= -0.391; *p*=0.024). Adropin ≥ 2.25 ng/ml was the best cut-off point to differentiate T2DM patients from healthy controls (sensitivity= 57.5%; specificity= 82.5%; positive predictive value=76.67%; negative predictive value=66%). We showed that T2DM patients have higher adropin levels, and serum level of adropin is inversely associated with insulin resistance; therefore indicating a close association between adropin and T2DM. However, further studies are necessary to establish the role of adropin in diabetes.

Key words: Diabetes Mellitus, Adropin, Insulin Resistance

1. INTRODUCTION

Type 2 Diabetes Mellitus (T2DM), the most common metabolic disease in all populations (1-3), is a costly disease and consume more than 8.69% of total health expenditure (3). T2DM is also considered as an independent risk factor for both microvascular and macrovascular problems (2, 4, 5). T2DM is characterized initially by two principal defects; insulin resistance and beta cell failure which eventually lead to glucose intolerance and hyperglycemia (1-3). However, the precise reason of how insulin resistance results in T2DM remains to be completely understood. Based on recent studies in humans and rodents, derangements of metabolic homeostasis are associated with mechanisms mediating insulin resistance (6-9). In recent years, much attention has

been focused on potential role of molecules involved in regulation of metabolic homeostasis and complicated interactions between its components in pathogenesis of T2DM. The metabolic homeostasis is principally modulated through the neuroendocrine incorporation of the central stress pathways to the CNS centers that control appetite and energy expenditure (6-9). Adropin is one of the recent discovered peptide hormones with protective roles involved in metabolic homeostasis, which is a product of the energy homeostasis associated (Enho) gene (6, 9, 10). Interestingly, based on animal studies, adropin is regulated by fasting and feeding but is not necessary for regulating food intake; though, it exerts functional roles in preventing insulin resistance, dyslipidemia, and impaired glucose tolerance in rodents (10). It has been demonstrated that tissue expression of adropin is higher in streptozotocin -induced diabetic rats compared with controls and pancreas and liver showed the highest expressionof adropin among the other organs (11). Although the precise functions of adropin are still unclear, clinical evidence indicated its roles on diseases related to abnormal metabolic hemostasis and also derangements of cardiovascular functions in humans. For instance, patients with cardiac syndrome X have low circulating levels of adropin (12); and decreased concentration of adropin is associated with obesity, aging ,insulin resistance and stable coronary artery disease (13, 14). Lower circulating levels of adropin in obese children (15) , in patients with acute myocardial infarction (16) and in obese adolescents with fatty liver disease are other examples in this regard (17). As summarized above, the primary findings on the functional roles of adropin in lipid metabolism, insulin resistance, and obesity in humans require more support. One major question to be answered is whether adropin circulating levels are altered in patients with T2DM. Also one may inquire into whether adropin can be an emerging diagnostic marker for diagnosis of T2DM. As far as we know there is insufficient information concerning the association of adropin with clinical characteristics in T2DM patients, excepting for limited studies (18, 19), we aimed to measure the serum levels of adropin in T2DM patients compared with healthy subjects and also study its association with diabetes-related characteristics.

2. MATERIALS AND METHODS

2.1. Study population

This case-control study was conducted on patients with T2DM (n=40) and healthy subjects (n=40). Patients were selected from individuals who consecutively attended the Diabetes Clinic of Imam Khomeini Hospital, affiliated with Tehran University of Medical Sciences, Tehran, Iran. T2DM was defined using American Diabetes Association (ADA) criteria (20).Controls were recruited from among healthy men who were visited by endocrinologists of the same clinic and were excluded if they had a history of diabetes mellitus in their first-degree relatives. It should be noted that all participants were men who had an age between 45 and 75 years and exclusion criteria for all were: any chronic liver and renal disease, any history of inflammatory, infectious, or malignant diseases. The study protocol was approved by Ethics Committee of Tehran University of Medical Sciences (TUMS) and all participants provided informed consents prior to study. Peripheral blood samples (10 ml) were taken after an overnight fast and collected clot tubes to separate serum. Individuals were categorized regarding their status of glycemic levels as controlled/uncontrolled based on ADA criteria (20): HbA1c < 7.0% or FBG < 130 mg/dl.

2.2. Measurements

Serum concentration of fasting blood glucose (FBG) were evaluated by the glucose oxidase method. Serum levels of triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), were assessed using the commercial kits (Pars Azmoon kits, Iran). Insulin levels were assessed by Immunoradiometric Assay (IRMA) kit (DIAsource., Belgium). HbA1c was measured by ion-exchange high performance liquid chromatography. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated using this formula: Fasting insulin (μU/mL) x Fasting glucose (mg/dL) /405. Serum Adropin levels were determined by ELISA kit (Phoenix Pharmaceuticals, Belmont, CA, USA). The linear range of this kit was from 0.3 to 8.2 ng/ml.

2.3. Statistical analysis:

Data are presented as mean ± standard deviation (SD) for normally distributed data based on Shapiro-Wilk test, while variables without normal distribution are presented as median (interquartile range: P25-P75). Differences were investigated by Student's t-test (for normally-distributed data) and Mann-Whitney U tests (for nonparametric data), where indicated. One-tailed Spearman's ρ correlation coefficient was used to explain correlations of characteristics. Receiver Operating Characteristic (ROC) curve was also plotted to evaluate adropin ability to differentiate T2DM and healthy individuals. Also binary logistic regression was performed to adjust the confounding effects of clinical and metabolic characteristics. Data were analyzed by IBM™ SPSS version 20 and *p*-values less than 0.05 were considered statistically significant.

3. RESULTS AND DISCUSSION

3.1. Demographic and Clinical Characteristics

The average age of patients and controls was 61.25 ± 6.94 years and 58.88 ± 7.31 years, respectively and there was no significant difference between them (p=0.14). There were significant differences regarding body mass index (BMI), waist to hip ratio (WHR), and central fat accumulation (CFA) of diabetic patients and healthy controls (Table 1).

Table 1. Anthropometric and Clinical Characteristics of T2DM patients and controls

Characteristics	Healthy Controls	T2DM	*p*-value
Age (yr)	58.88 ± 7.31	61.25 ± 6.94	0.140
BMI (kg/m^2)	23.21 ± 0.58	25.62 ± 3.68	**<0.001**
BMI ≥ 25 kg/m^2	0 (0%)	16 (40%)	**<0.001**
WC (cm)	85.12 ± 2.43	89.23 ± 3.31	**<0.001**
HC (cm)	93.41 ± 1.05	92.69 ± 0.94	**0.002**
WHR	0.91 ± 0.03	0.96 ± 0.04	**<0.001**
CFA (%)	27 (67.5%)	38 (95%)	**0.002**
FBG (mg/dl)	80 (72-87)	108 (87-132)	**<0.001**
Insulin (mU/l)	9.35 (7.7-14)	14.75 (12-22)	**<0.001**
HOMA-IR	1.81 (1.41-2.63)	4.57 (3.53-7.28)	**<0.001**
HbA1c (%)	4.88 ± 0.85	8.17 ± 1.79	**<0.001**
HDL-c (mg/dl)	44 (38-49)	31 (25-36)	**<0.001**
LDL-c (mg/dl)	102 (88-112)	70 (49- 98)	**<0.001**
TG (mg/dl)	144 (101-175)	150 (105- 188)	0.567
TC (mg/dl)	135 (114-151)	136 (105-160)	0.725

Continuous variables are described as mean ± SD for normally distributed data, but non-parametric variables are presented as median (interquartile range: P25-P75). Categorical variables are described as frequencies.
Differences between cases and controls are obtained based on Student's t-test or Mann-Whitney U test, where indicated for continuous variables. Chi-square test was performed for categorical variables.
BMI, Body Mass Index; WC, Waist Circumference; HC, Hip Circumference; WHR, waist to hip ratio;
CFA (central fat accumulation) was defined as WHR ratio ≥ 0.9
FBG, Fasting Blood Glucose; HbA1c, Glycated Hemoglobin;
LDL-c, Low Density Lipoprotein Cholesterol; HDL-c, High Density Lipoprotein Cholesterol;
TG, Triglyceride; TC, Total Cholesterol; T2DM, Type 2 Diabetes Mellitus
HOMA-IR, Homeostatic Model Assessment of Insulin Resistance

Although only 40% of recruited men with T2DM were overweight as compared to healthy men (0%; p<0.001), CFA was significantly higher in T2DM (OR = 9.148 95% CI = 1.906-43.898; p=0.002). T2DM patients had expectedly significantly higher FBG, HbA1C, insulin, and HOMA-IR levels compared to healthy controls (p<0.001). It should be mentioned that disease duration of T2DM was 4.75 (2.75-8) years and 80% of patients were under statin therapy, while healthy controls were not. Healthy controls had statistically significant higher HDL and LDL levels compared to diabetic patients, however there were no significant differences between total cholesterol and triglyceride of cases and controls. It should be noted that 25 (62.5%) of patients used glibenclamide while the remaining patients were under metformin regimen. Only 30% of T2DM patients had HbA1c<7%, but 75% of them showed FBG<130 mg/dl.

3.2. Adropin Levels

We observed that serum adropin levels of T2DM patients were significantly higher than healthy controls (Median ± IQR; patients: 2.5 ± 1.28; controls: 1.9 ± 0.6; p=0.004) (Figure 1).

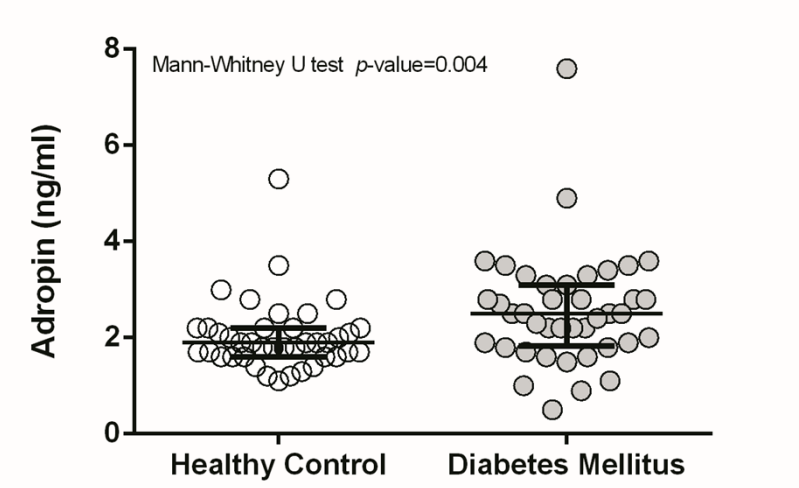

Figure 1. Adropin levels of T2DM patients and healthy controls were significantly (p=0.004) different

3.3. Adropin and clinical/metabolic characteristics

Receiver operating characteristic (ROC) curve (Figure 2) was provided to determine the diagnostic abilities of adropin in differentiation of T2DM patients from healthy controls.

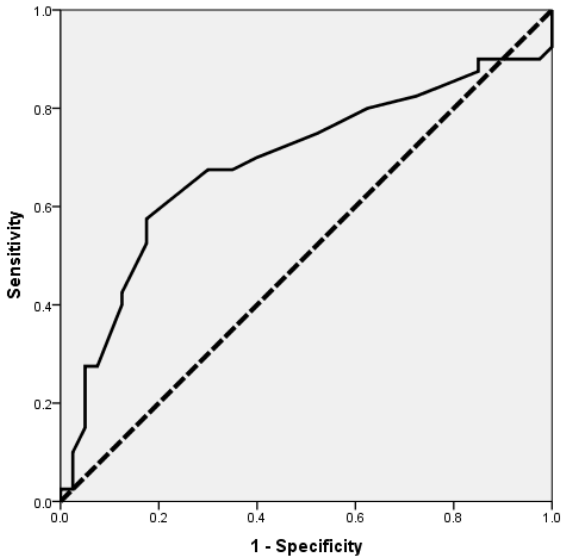

Figure 2. Receiver operating characteristic (ROC) curve regarding the diagnostic abilities of adropin in differentiation of T2DM patients from healthy controls is depicted. Area under the curve (AUC) of ROC curve was 0.688 (95% CI: 0.568-0.809) (*p*=0.004).

Area under the curve (AUC) of ROC curve was 0.688 (95% CI: 0.568-0.809) (*p*=0.004). As a byproduct for this study, we observed a cut-off of 2.25 ng/ml (sensitivity= 57.5%; specificity= 82.5%; positive predictive value=76.67%; negative predictive value=66%) as the best point in ROC curve for diabetes mellitus detection. Adropin did not show any associations with neither FBG nor clinical/metabolic variables in healthy controls; however, it showed significant inverse correlation with FBG in T2DM patients (Spearman's ρ= -0.335; *p*=0.017). More interestingly, this association was more prominent in T2DM patients when adropin was higher than 2.25 ng/ml (Spearman's ρ= -0.619; *p*=0.001). We observed that only in T2DM patients without intensive glycemic control (HbA1c≥7%), adropin was negatively correlated with FBG (Spearman's ρ= -0.382, p=0.022). Also we found a mild negative correlation between HOMA-IR and adropin of T2DM patients (Spearman's ρ= -0.391, p=0.024). Adropin was also negatively correlated with LDL-c in the total study population (Spearman's ρ= -0.292, p=0.004). It is of particular importance that the association between adropin and T2DM was not confounded by clinical and metabolic characteristics (Table 2).

Table 2. Binary Logistic Regression was conducted to adjust the effects of clinical and metabolic characteristics of studied population. The association between adropin and T2DM was not confounded by those variables.

Characteristics	B	SE	Wald	*p*-value	OR	95% CI for OR	
						Lower	Upper
Univariate Model							
Adropin ≥ 2.25 ng/ml	1.853	0.525	12.463	**<0.001**	6.378	2.280	17.842
Adjustment for FBG							
Adropin ≥ 2.25 ng/ml	1.867	0.628	8.824	**0.003**	6.467	1.887	22.164
FBG	0.073	0.021	11.805	**0.001**	1.076	1.032	1.122
Adjustment for LDL-c							
Adropin ≥ 2.25 ng/ml	1.658	0.615	7.265	**0.007**	5.248	1.572	17.519
LDL-c	-0.056	0.014	15.091	**<0.001**	0.946	0.919	0.973
Adjustment for HbA1c							
Adropin ≥ 2.25 ng/ml	2.247	0.986	5.192	**0.023**	9.462	1.369	65.382
HbA1c	2.493	0.734	11.537	**0.001**	12.097	2.870	50.980
Adjustment for HOMA-IR							
Adropin ≥ 2.25 ng/ml	2.961	1.231	5.787	**0.016**	19.311	1.731	215.494
HOMA-IR	1.940	0.646	9.019	**0.003**	6.961	1.962	24.698
Adjustment for WHR							
Adropin ≥ 2.25 ng/ml	2.051	0.682	9.048	**0.003**	7.779	2.044	29.607
WHR	52.45	12.87	16.599	**<0.001**	6.02×10^{22}	6.63×10^{11}	5.48×10^{33}

FBG, Fasting Blood Glucose; LDL-c, Low Density Lipoprotein Cholesterol;
HbA1c, Glycated Hemoglobin; WHR, Waist to Hip Ratio
HOMA-IR, Homeostatic Model Assessment of Insulin Resistance

This is study tries to understand the role of the peptide hormone, adropin, in men with T2DM. The main findings can be summarized into: 1) adropin levels were significantly higher in T2DM compared to healthy individuals; 2) In T2DM patients adropin was inversely associated with FBG (only in patients with HbA1C≥7%) and was also negatively correlated with HOMA-IR. 3) we observed a fair diagnostic characteristic (sensitivity= 57.5%; specificity= 82.5%; positive predictive value=76.67%; negative predictive value=66%) when

circulating level of adropin was equal or more than 2.25ng/ml. Recently, Ugur et al discovered that seum and urine adropin levels are significantly higher indiabetic patients compared to healthy controls (19), which is in line with our finding regarding the higher adropin in serum of men withT2DM. However, studies on adropin-deficient mice shows that this peptide hormone is necessary for metabolic homeostasis, which exerts its role for maintaining insulin sensitivity and preventing dyslipidemia and protecting against impaired glucose tolerance (13). Administration of recombinant adropin has been demonstrated to reverse insulin resistance and dyslipidemia in mice (9). Recent study of Gao et al (21) demonstrated that adropin treatment of diet-induced diabetic mice enhances glucose tolerance, improves insulin resistance and enhances preferential carbohydrate metabolism over lipid metabolism in the context of energy selection. They suggested that skeletal muscle is the pivotal peripheral tissue in mediating adropin effects, in which adropin exerted its protective role by sensitizing insulin signaling pathways and substituting glucose instead of fat in muscle as the energy source, while it was shown to suppress fat oxidation (21). Kumar et al showed that in adropin knockout mice, adropin deficiency exhibits negative effects on glucose homeostasis; in the other words, adropin deficiency was associated with attenuated suppression of endogenous glucose production by insulin (10). They suggested that the partial insulin resistance in adropin knockout mice is due to impaired suppression of endogenous glucose production, and adropin is important for this insulin-mediated non-hepatic mechanism of preventing insulin resistance (10). Because of the mentioned protective effects of adropin, our results of higher levels of adropin in T2DM patients in comparison with healthy subjects might, firstly, seem to be in contrast with previous evidence indicating lower adropin circulatory levels in obese subjects and in coronary artery disease patients with diabetes (13, 22). Our findings which are obtained from a homogeneous sample of men with T2DM, are consistent with the similar study on T2DM patients (19) and indicate a higher level of adropin in these patients in comparison with healthy individuals. Since it is demonstrated that adropin deficient mice have increased body weight due exclusively to increased fat mass (10), one may assume that adropin, here, is high at least in part because only 40% of T2DM patients were overweight; however, we did not observe any association between BMI and adropin concerning the subgroups of overweight/normal as well as continuous levels. Also the fact that the reversal of obesity and metabolic syndrome after Roux-en-Y gastric bypass leads to increased adropin levels favors this concept (13). Aydin et al (11) discovered that adropin levels are increased in streptozotocin-induced diabetic rats, which might be in line with our findings regarding the higher levels of adropin in T2DM patients. Moreover, adropin treatment in diet-induced obese mice was found to reduce defective fatty acid oxidation and augmented CoA/acetyl-CoA ratio, which indicate improved mitochondrial function on lipid metabolism (21). The underlying mechanisms for anti-hyperlipidemic effects of adropin seem to be involved in suppressions of carnitine palmitoyltransferase-1B and CD36, which are two central enzymes in fatty acid metabolism (21). Actually, we found out T2DM patients with normal weights produce more adropins, and their adropin levels were inversely correlated with FBG when their HbA1C is higher than 7% (which denotes poor glycemic control). Also these increased adropin levels were found to be associated with decreased FBG and HOMA-IR levels. Altogether these data might support the protective roles of adropin through insulin-mediated suppression of endogenous glucose production (10) and its protection against glucose intolerance (21). Similarly, serum adropin levels was inversely correlated with HOMA-IR in patients with polycystic ovarian syndrome (23). Gao et al (21) showed that in muscle of diet-induced obese mice adropin treatment increases insulin-mediated Akt phosphorylation and augments GLUT4 cell-surface expression, also adropin treatment activates pyruvate dehydrogenase (PDH, a rate-limiting enzyme in glucose oxidation) and down-regulates PDH kinase-4 which is an inhibitor of PDH. Altogether, these evidence, in line with the inverse association we observed for FBG/HOMA-IR and adropin in T2DM patients suggests that adropin might exert its anti-hyperglycemic roles through sensitization of insulin signaling pathways (21). Moreover, the increased adropin in T2DM might be due to a feedback mechanism or in response to their medications. Moreover logistic regression analysis showed us the observed levels of adropin in T2DM and healthy individuals are not statistically confounded by their metabolic or clinical variables (LDL-c, FBG, HbA1C, HOMA-IR), which might indicate that adropin *per se* is an independent peptide hormone involved in lipid metabolism and glucose homeostasis. Also the study of Aydin et al (11) demonstrated not only liver is not the only source of adropin, but also pancreas (serous acini) is a more prominent source of adropin production in rats. Thus the primary source of this peptide hormone, pancreas, might be another indication for importance of adropin as an endocrine hormone involved in various metabolic pathways. These data show that T2DM patients with normal weights have higher adropin levels, which seem to be a feedback response to high glucose levels or a response to the anti-diabetic medications.

4. CONCLUSION

Our study emphasizes the significance of adropin in maintaining glucose homeostasis and regulation of lipid metabolism; and provides information for future prospective and interventional human studies to assess adropin therapeutic roles in human individuals with T2DM.

ACKNOWLEDGMENT

We are highly thankful to the Tehran University of Medical Sciences for financial support of this study (study number: 21419-30-02-92). We also appreciate staffs of Diabetes Clinic of Imam Khomeini Hospital for their helpful cooperation.

FUNDING/SUPPORT

Not mentioned any Funding/Support by authors.

AUTHORS CONTRIBUTION

This work was carried out in collaboration among all authors.

CONFLICT OF INTEREST

The authors declared no potential conflicts of interests with respect to the authorship and/or publication of this article.

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