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Correlations of Neuropeptide Y and Adiponectin Serum Levels in Obese Type 2 Diabetics in Relation to Insulin Resistance

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ABSTRACT

Background: The importance of obesity in the progression of Type 2 Diabetes Mellitus (T2DM) is represented by defective biochemical markers' production and release that may interact with each other, resulting in negative outcomes for the diabetic state. When neuropeptide Y is released and interacts with adipose tissue, it may affect the adiponectin release, which plays a role in glucose metabolism and insulin sensitivity.
Objectives: To estimate the serum levels of neuropeptide-Y and its impact on adiponectin release in obese T2DM patients in relation to the insulin resistance state.
Materials and methods: Eighty-seven T2DM patients attending the clinic of the National Center of Diabetes Treatment and Research, Baghdad, Iraq, were categorized into two groups; Group 1: 45 obese T2DM patients with BMI of $\geq$ 30 kg/m^2 and age 31–59 years, and Group 2: Normal body weight T2DM patients with BMI of 18.5–24.9 kg/m^2, included 42 patients, with an age 33–60 years. Fasting blood specimens were utilized to measure serum neuropeptide-Y, adiponectin, and glycemic markers for each participant.
Results: The fasting blood glucose (FBG), glycated hemoglobin (HbA1c), Homeostasis Model Assessment Insulin Resistance (HOMA-IR), and neuropeptide-Y values were significantly elevated (P-value = 0.001) in Group 1 in comparison with Group 2. Serum insulin and adiponectin levels were significantly higher (P-value = 0.001) in Group 2 compared to Group 1. Furthermore, serum neuropeptide-Y, FBG, HbA1c and HOMA-IR were negatively correlated with adiponectin serum levels, where (rho = -0.617, P-value = 0.001), (rho = -0.684, P-value = 0.001), (rho = -0.359, P-value = 0.001), and (rho = -0.271, P-value = 0.011) for neuropeptide Y, FBG, HbA1c and HOMA-IR, respectively, while the fasting serum insulin was positively correlated with adiponectin serum level (rho = 0.310, P-value = 0.003).
Conclusion: Elevated serum neuropeptide-Y and declined adiponectin levels in obese as compared with normal-weight diabetic patients may reflect the negative impact of serum levels of neuropeptide-Y- on adiponectin release. Furthermore, adiponectin levels were negatively correlated with glycemic markers; which is an indication of its beneficial role in T2DM improvement.
Keywords: Adiponectin; Neuropeptide Y; Obesity; Type 2 diabetes mellitus.

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) accounts for around 90% of all cases of diabetes [1]. Hyperglycemia, resulting from low insulin levels, insulin resistance, or both, characterizes this chronic condition [2]. Obesity is considered the risk factor for the development of insulin resistance and a significant element in the etiology of T2DM [3]. It has been simply defined as an unusual or extreme accumulation of body fat [4]. Adipose tissue is a key part of the pathophysiology of T2DM because it releases free fatty acids and works as an endocrine organ that releases different adipokines. Different adipokines secreted by adipose tissue act as mediators between obesity and insulin resistance [5]. Adiponectin (APN), a specific adipokine found in adipose tissue, plays a crucial role in combating inflammation and insulin resistance, while also offering protection

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against metabolic disorders [6].

Neuropeptide Y (NPY) is one of the most powerful orexigenic peptides, produced in large amounts by the hypothalamus as well as in peripheral adipose tissue [7]. NPY exerts its effects by interacting with its receptors (NPYRs), which are six isoforms [8]. It interacts with adipocytes through its binding with Y1 and Y2 receptors [9].

There is a potent association of NPY with obesity, where it is the most powerful orexigenic peptide that can induce obesity, and also because it can be produced by adipose tissue, making it as a targeted biomarker in research about obesity and its complications. To the best of our knowledge, no locally relevant study has yet explored the relationship between NPY and APN, particularly in the context of obese T2DM and insulin resistance. This study's goal was to look at the amount of NPY in the serum and how it affects the release of APN. It also wanted to see how these changes affect insulin resistance and other signs of T2DM in obese people.

MATERIALS AND METHODS

A cross-sectional study was conducted at the National Center for Diabetes/College of Medicine, Mustansiriya University, from 15 October 2023 to 25 January 2024. A total of eighty-seven T2DM patients aged between 31-60 years (39 male and 48 female) were selected according to the criteria specified below from the out-patient clinic under the supervision of an endocrinologist from patients attending the center. The American Diabetes Association's criteria guided the diagnosis of diabetic subjects [10]. According to these diagnostic criteria, the patients were diagnosed to be diabetic when FBG ≥7.0 mmol/L (126 mg/dL) or HbA1c ≥ 6.5% (48 mmol/mol) or 2-hour plasma glucose ≥ 11.1 mmol/L (200 mg/dL) during an oral glucose tolerance test or in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥ 11.1 mmol/L (200 mg/dL). The diagnosed patients were then divided into two groups according to their body mass index (BMI): Group-1: Obese T2DM patients with a BMI ≥ 30 kg/m^2, included 45 patients (19 male, 26 female); Group-2: Normal weight T2DM patients with a BMI of 18.5-24.9 kg/m^2, included 42 patients (20 male, 22 female).

The Ethics Committee of the College of Pharmacy, University of Baghdad (Reference number RECAUBCP 22102023) approved the study. Informed consent was taken from each participant after being informed about the purpose of the study and the expected benefits. They were asked about their age, sex, duration of T2DM, and past medical history. The BMI was calculated according to the following equation: weight (kg)/height (m^2), an individual is considered normal weight if BMI is (18.5–24.9), and obese if it is ≥ 30 [11].

Inclusion criteria

The patients were selected to have T2DM (diabetes duration > 1 year) for both male and female patients. They must be at least 18 years old and have a BMI between 18.5 and 24.9 for normal weight and ≥ 30 for obese patients. Exclusion criteria: The patients having any other endocrinopathy, or those with chronic liver diseases, renal diseases, malignant diseases, or on insulin therapy, or on drugs that affect serum levels of NPY (anti-depressant, antipsychotic, anti-hypertensive, antiplatelet, and anti-obesity drugs), chronic use of non-steroidal anti-inflammatory drugs (NSAID), alcohol, and cocaine, or drugs that affect serum levels of APN (thiazolidinediones, lipid-lowering agents, and corticosteroids), pregnant and lactating women, and those who declined to participate were excluded from the study.

Venous fasting blood samples (6 mL) were drawn from each patient. A fresh blood specimen (1 ml) was added to EDTA-tubes for measuring HbA1c [NycoCard HbA1c Test Kit/Abbott Co. /USA/ 1116813] in the blood by boronate affinity assay using the NycoCard Reader II. The remainder of the blood specimen was left at room temperature in a gel-containing tube for 30 minutes to complete clotting and then to be centrifuged at 4000 rpm for 10 minutes. Serum was separated and transferred into Eppendorf tubes and stored at -20°C until the time of measuring fasting serum insulin [Insulin (INS) Human ELISA Kit/Wuhan USCN Business Co., Ltd/ China/CEA448Hu], NPY [Human Neuropeptide Y/Elabscience Biotechnology Co., Ltd./China/E-EL-H1893] and APN [Adiponectin (ADP) human ELISA kit/Wuhan USCN Business Co., Ltd./ China/SEA605Hu] levels by enzyme-linked immuno-sorbent assay (ELISA), while FBG [GLUCOSE/BioSystems Co./Spain/11503], high density lipoprotein cholesterol (HDL-C)[CHOLESTEROL HDL/ BioSystems Co./Spain/11523], total cholesterol (TC)[CHOLESTEROL/BioSystems Co./Spain/11505], and triglycerides (TG)[TRIGLYCERIDES/BioSystems Co./Spain/11528] were measured by colorimetric assay. Low-density lipoprotein-cholesterol (LDL) levels are estimated using the Friedewald formula [12].

LDL (mg/dL) = TC – (HDL + TG/5) Where (TG/5) represents the very low-density lipoprotein (VLDL) in mg/dL. where the normal levels for TC <200 mg/dL, TG <150 mg/dL, HDL >60 mg/dL, LDL <130 mg/dL and VLDL <30 mg/dL Insulin resistance was calculated based on the homeostasis model assessment of insulin resistance (HOMA-IR) equation [13].

HOMA-IR= [(FBG (mg/dL) × fasting insulin (μU/mL))/404], where HOMA-IR values between 0.5 and 1.4 are considered normal. The normal range for fasting insulin levels (5-15) μU/mL, APN (3–30) μg/ml, and NPY (154–513) pg/ml.

Sample size calculation

The sample size was calculated according to the following equation [14].

n= Z^2 P (1- P)/d^2

Where: n = sample size, Z = differential coefficient = 1.96, d = estimated error < 0.05, and P = prevalence of T2DM in Iraq from a previous study (8.5%) [15]. n = (1.96)2 × 0.085 × (1-0.085)/ (0.05)2. According to this equation, the sample size was equal to 120 patients, but because of the challenging criteria that have been established for the identification of the most suitable subjects for the study, in addition to the limited study time and study cost, only 87 samples were collected.

Statistical Analysis

Statistical analysis was performed by Statistical Package for Social Science (SPSS, version 24, USA) for Windows. The uniformity of the data distribution of the variables was checked via the Shapiro-Wilk test; the P-values for measured data were less than 0.05, which means the data were not normally distributed, thus non-parametric tests were used for data analysis. The descriptive statistics for continuous variables defined as [median and interquartile range (IQR)] and

the difference between these data of the two groups were checked by the Mann-Whitney U test, while the categorical variables were expressed as frequencies and percentages, and the difference between groups was checked using the Chi-square test. Spearman's correlation coefficient (rho) was run to find out the statistically significant correlations between measured parameters. P-value < 0.05 was considered a statistically significant difference.

RESULTS

The age range of the participants who were enrolled in this study was 31–59 years in the obese patients' group, and the median was 50 years (IQR=13 years), while in the normal weight group, the age range was (33–60) years and the median was 52 years (IQR=21 years) with no significant difference between the two groups (P-value = 0.717). Out of 45 obese diabetes patients, 19 (42.22%) were males and 26 (57.78%) were females, while out of 42 normal weight diabetic patients, 20 (47.62%) were males and 22 (52.38%) were females, with no significant difference between the two groups (P-value = 0.615). There was a statistically significant difference between the two study groups with regard to BMI, which was significantly higher (P-value = 0.001) in the T2DM obese group than in the T2DM normal weight group. The obese diabetics have higher HbA1c and higher levels of FBG compared to the normal-weight patients, with significant variations between the two groups (P-value = 0.001). According to HOMA-IR, there were significant differences between the obese and normal-weight diabetic patients, with the obese group having the higher value (P-value = 0.001). However, serum insulin levels showed a higher value in normal-weight patients than in obese diabetic patients (P-value = 0.001). There are no significant differences in serum TC, TG, LDL, VLDL, and HDL between the two studied diabetic groups (P-value > 0.05). Serum levels of APN were significantly lower (P-value = 0.001) among participants in the obese group, where the median was 2.16μg/ml (IQR=0.57μg/ml) and in those in the normal weight group the median was 4.08μg/ml (IQR=0.87μg/ml). On the other hand, serum levels of NPY were significantly higher (P-value = 0.001) among participants in the obese group, the median=167.14pg/ml (IQR=50.90pg/ml) compared to those in the normal weight group, the median=116.07pg/ml (IQR=19.916pg/ml) as shown in Table 1.

Serum APN levels showed a significant negative correlation with BMI, HbA1c, FBG, and HOMA-IR, while it has a positive correlation with fasting serum insulin. Whereas, serum NPY levels showed a significant positive correlation with BMI, HbA1c, FBG, and HOMA-IR, and it has a negative correlation with fasting serum insulin. Additionally, there is a significant negative correlation between NPY and APN (rho = -0.617, P-value = 0.001) as shown in Table 2.

Table 1. Demographic and Biochemical Characteristics of Participants.[†]

Variables	Normal weight N = 42	Obese N = 45	P-value
Age (years)	52 (21)	50 (13)	0.717
Sex			
Male	20 (47.62%)	19 (42.22%)	0.615
Female	22 (52.38%)	26 (57.78%)	
Duration of DM (years)	5 (8)	3 (3)	0.097
BMI (kg/m^2)	23.95 (1.83)	33.2 (4.25)	0.001*
HbA1c (%)	6.8(1.38)	8.76(3.07)	0.001*
FBG (mg/dL)	126.49(13.10)	190.74(40.56)	0.001*
Fasting Insulin (μU/ml)	2.911(0.538)	2.148(0.94)	0.001*
HOMA-IR	0.86(0.33)	1.04(0.53)	0.001*
TC (mg/dL)	183.31(23.49)	179(23.65)	0.220
TG (mg/dL)	163.55(27.21)	153.5(29.37)	0.077
HDL (mg/dL)	41.54(5.84)	43.5(6.20)	0.465
LDL (mg/dL)	106.56(24.79)	107.67(23.98)	0.322
VLDL (mg/dL)	32.71(5.44)	30.70(5.87)	0.077
NPY (pg/ml)	116.07(19.916)	167.14(50.90)	0.001*
APN (μg/ml)	4.08(0.87)	2.16(0.57)	0.001*

[†] The Chi-square test was used in the comparison of gender and the Mann-Whitney U test was used in the comparison of other variables, the expression of values in a table as [median (interquartile range)], N: number of patients, BMI: body mass index, HbA1c: glycated hemoglobin, FBG: fasting blood glucose, HOMA-IR: Homeostatic Model Assessment for Insulin resistance, TC: total cholesterol, TG: triglyceride, HDL: high-density lipoprotein, LDL: low-density lipoprotein, VLDL: very low-density lipoprotein, NPY: neuropeptide Y, APN: adiponectin, and (*) refers to a significant difference.

Table 2. Correlations of serum levels of APN and NPY with the studied variables in the total participants.[†]

Variables	APN (µU/ml) N = 87, rho	NPY (pg/ml) N = 87, rho
Age(years)	0.057	-0.063
Gender(m/f)	0.048	0.167
Duration(years)	0.150	-0.209
BMI (kg/m^2)	-0.685***	0.670***
HbA1c%	-0.359**	0.274**
FBG (mg/dL)	-0.684***	0.697***
Fasting insulin (µU/ml)	0.310**	-0.296**
HOMA.IR	-0.271*	0.301**
APN(µg/ml)		-0.617**

[†] The correlation tested by Spearman Correlation test, N: number of patients, BMI: body mass index, HbA1c: glycated hemoglobin, FBG: fasting blood glucose, HOMA-IR: Homeostatic Model Assessment for Insulin resistance, NPY: neuropeptide Y, APN: adiponectin, (*) refers to significant difference If P-value < 0.05, (**) If P-value < 0.01, and (***) if P-value < 0.001) and rho is spearman's correlation coefficient.

DISCUSSION

Adipose tissue can produce NPY, which interacts with it and disrupts its function [8, 9]. The most common adipokine, Adiponectin, is associated with insulin sensitivity and offers protection against metabolic disorders [6]. The results of the study were high NPY and low APN serum levels in obese patients, in addition to the negative correlation between these two markers.

According to the criteria used to choose the study's participants, there were no differences in the groups' age, gender, or duration of diabetes. This eliminated the possibility that any of these variables might have an impact on the studied biomarkers.

In Thailand, a study conducted by Sitticharoon et al. on obese healthy subjects described significantly higher serum

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NPY levels in obese women compared to normal-weight subjects [16], and in a Chinese study conducted by Tang et al. on obese individuals that have metabolic abnormalities vs. healthy obese, it was indicated that higher serum NPY levels were found in only obese individuals that have metabolic abnormalities [7]. The results of these two studies were similar to the current study. A Turkish study by Guzelkas et al. observes the high NPY levels in both obese and non-obese patients with polycystic ovarian syndrome (PCOS), and it's not associated with body weight [17]. The difference in sample size, study design, age range, and genetic and demographic characteristics of diverse populations can lead to different outcomes across studies. However, the elevated NPY serum levels in obese subjects may make targeting it a potential therapeutic approach for obesity management, particularly focusing on reducing appetite and food intake in obese individuals [7].

Obesity is associated with the initiation of a chronic state of inflammation, which leads to the alteration of macrophage's inflammatory profiles in adipose tissue. Despite the response of numerous neuro-humoral elements, chronic stress and sympathetic nervous system activation primarily elevate NPY, a principal hormone [18]. According to some observations, the source of this elevated NPY is the myeloid cells within adipose tissue, which are considered a regulated non-neuronal source of NPY production [18]. Another study indicated that NPY can be secreted by adipocytes located in visceral adipose tissue in obese participants with hyperlipidemia [7].

The serum APN level in this study was lower in the obese patient's group compared to the normal-weight patients' group, and it has a negative correlation with BMI. Shirazi et al., observed that obese PCOS patients had lower levels of APN [19]. Abed et al. indicated a highly significant decrease in APN levels in the obese diabetic group compared to the non-obese group [6]. Mahmood et al., also indicated that serum levels of APN were significantly lower in obese patients than in healthy control [20].

Although many mechanisms have been suggested, no one exactly described the feedback mechanism in APN regulation. Despite numerous suggestions, the precise description of the feedback mechanism in APN regulation remains elusive. Obesity directly prevents APN transcription through noticeably increased levels of inflammatory cytokines and leptin [21]. In addition, an increase in visceral fat mass leads to a reduction in systemic APN levels. The lowered APN levels have no regulatory control over the elevated insulin that is stimulated by glucose signaling. Therefore, there is an augmented transformation of glucose and glycogen into fats, which are taken up by the skeletal muscles, leading to intramuscular fat buildup. Subsequently, a malicious series is initiated where increased adiposity causes a drop in APN levels [21].

Data analysis of this study indicated a significant negative correlation between NPY and APN of the total participants. De Piano et al., established the evidence of the correlation between hypo-adiponectinemia and higher NPY/AgRP (Agouti-Related Protein is neurons in the arcuate nucleus of the hypothalamus, which co-express NPY) [22]. While, Nway et al., demonstrated that in subcutaneous adipose tissue, the APN expression positively correlated with that of subcutaneous NPY [23], which disagrees with the outcome of this study. The different medium in which these molecules are measured (serum levels in this study vs. tissue levels in Nway et al., study) could explain the variation between the results.

NPY does not directly decrease APN release. Instead, NPY is known to help make adipocytes and stop lipolysis (the breaking down of fats) in adipose tissue. This can have an indirect effect on APN levels by changing the makeup and function of adipose tissue. However, our understanding of the specific mechanisms by which NPY might influence APN release remains incomplete [24].

The data analysis of this study also indicated that the FBG, HbA1c, and HOMA.IR values were higher in obese patients, and they have a significant negative correlation with serum APN levels, while the fasting serum insulin levels were higher in normal-weight patients, and it is positively correlated with APN serum level. Abed et al., observed a negative correlation between FBG, HbA1c, and HOMA.IR with serum APN in obese diabetic patients [6]. Wang et al. showed a negative correlation between serum APN levels and HOMA-IR in patients with T2DM [25].

APN plays a role in the improvement of insulin resistance where it has anti-inflammatory properties that reduce inflammatory reactions which are caused by pro-inflammatory adipokines produced by adipose tissue in an obesity state that result in direct augment insulin resistance and thus causing disrupted insulin sensitivity. Researchers have also reported that it prevents inflammatory cytokine-induced apoptosis from killing cultured cells and maintains both cell mass and glucose homeostasis in a mouse model of type 1 diabetes mellitus [26]. Researchers have reported that APN enhances glucose utilization in myocytes, enhances hepatic and systemic insulin resistance in hepatocytes, and inhibits both glycogenolysis and gluconeogenesis by reducing the rate-limiting enzymes for hepatic glucose production [26].

Obesity, mainly the visceral type, has been related to insulin resistance development with consequent T2DM development. NPY can interact with adipocytes and might influence the expression of adiponectin leading to lowered levels that might aggravate the insulin resistance state arising from obesity, leading to alleviating the role of APN as an anti-inflammatory activity and enhancing insulin sensitivity. Furthermore, adipocytes located in visceral adipose tissue in obese subjects can secrete NPY, potentially exacerbating their condition. These findings have a clinical impact, emphasizing the importance of addressing obesity through lifestyle modification before considering the associated consequences of metabolic disorders [7].

The relatively low number of patients in the study groups is one limitation of the present study. Other limitations are a brief study period and the study's execution in a single Iraqi center. Additionally, individual variations in diet, exercise, and sleep habits that can influence the measured biochemical markers were not considered.

CONCLUSION

Elevated serum NPY and decreased APN levels in obese T2DM patients as compared with normal-weight diabetic patients reflect that NPY may have a negative impact on APN release. Furthermore, APN levels are negatively correlated with glycemic markers including HOMA-IR, which is indicative of its beneficial effect on T2DM improvement. A large-scale, countrywide, multicenter study is required to confirm the findings of this study. Studying the expression of NPY receptors and its relation to APN expression in adipose tissue also may be needed to understand the exact action of NPY in adipocytes.

ETHICAL DECLARATIONS

Acknowledgments

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Ethics Approval and Consent to Participate

The study was approved by the Ethics Committee of the College of Pharmacy, University of Baghdad (Reference number RECAUBCP 22102023). Informed consent was obtained from each participant after being informed about the purpose of the study and the expected benefits.

Consent for Publication

Not applicable (no individual personal data included).

Availability of Data and Material

Data collected during this study are available from the corresponding author upon reasonable request.

Competing Interests

The authors declare that there is no conflict of interest.

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Authors' Contributions

All stated authors contributed significantly, directly, and intellectually to the work and consented it to be published.

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