Journal of Research in Pharmacy

Research Article

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Investigating the correlations between substance P, antioxidant levels, and metabolic markers in non-obese Type 2 Diabetic patients

Shahad Wisam AHMED*, Shatha Hussein ALI

Department of Clinical Laboratory Science, College of Pharmacy, University of Baghdad, Baghdad, Iraq
*Corresponding Author. E-mail: Shahad.ahmed2200m@copharm.uobaghdad.edu.iq (S.A.); Tel. +964 770 315 0820

Received: 22 July 2024 / Revised: 29 August 2024 / Accepted: 31 August 2024

ABSTRACT: Hyperglycemia and hyperinsulinemia in type 2 diabetes mellitus (T2DM) result in complications exacerbated by oxidative stress, leading to cardiovascular, nephropathic, neuropathic, and retinopathic complications. Substance P (SP), a natural neuropeptide, inhibits cell death and enhances cell growth during oxidative or inflammatory stress, suggesting a potential role in reducing diabetic complications. The current study aimed to investigate serum levels of total antioxidant status (TAS), SP, glycemic measures, and lipid profiles in non-obese T2DM patients and evaluate the correlations involving these biomarkers in a case-control study involving eighty-five adult participants (46 males and 39 females), aged (30-60) years, and were divided into two groups; 53 non-obese T2DM patients, **and** 32 Apparently healthy individuals of matching age, sex and body mass index to the patients group. The results showed that patients' glucose levels increased as a percentage increase of (>141%), mild elevated insulin levels (>50%), higher insulin resistance (>250%), the lipid parameters exhibited disruption comparing to the control group, in the diabetic group, the serum levels of TAS, SP decreased considerably in comparison to the control group. As evidenced by the outcomes; the TAS showed significant negative correlations with fasting serum glucose and low-density lipoprotein and positive correlations with high-density lipoprotein. Neither the glycemic indices nor the lipid profiles or TAS demonstrated any notable associations with SP levels. This suggests that while SP levels are reduced in T2DM patients, they do not appear to be directly linked with the measured biomarkers.

KEYWORDS: Lipid profile; Oxidative stress; Substance P; Total Antioxidant Status; T2DM

1. INTRODUCTION

Diabetes mellitus is a metabolic condition that involves a continuous rise in blood glucose levels and disruption in the metabolizing process of proteins, lipids, and carbohydrate [1–3] . Prolonged hyperglycemia causes serious consequences to several organs, such as peripheral neuropathy, nephropathy, which results in kidney failure, cardiovascular complications, and retinal degeneration that impairs vision [4,5]. After a long period of uncontrolled hyperglycemia, complications of diabetes develop, cardiovascular disease is more common in those who have type 2 diabetes (T2DM). as a result of a condition known as atherogenic dyslipidemia [6]. Coronary artery disease, specifically myocardial infarction, is the main contributor to morbidity and mortality among individuals with diabetes worldwide [7] .

Hyperglycemia results in the generation of reactive oxygen species (ROS) and the occurrence of oxidative stress inside mitochondria; however, their strong chemical reactivity makes them susceptible to cause destruction of large molecules such as lipids, proteins, and nucleic acids; Therefore, cells initiate protective mechanisms that control the generation of these ROS and prevent oxidative damage [8].

Substance P which interacts with neurokinin receptor 1 (NK-1R), it has been demonstrated that SP inhibits cellular alterations and promotes cell proliferation while preventing apoptosis in response to oxidative or inflammatory stress [9]. SP has been shown to enhance the inflammatory response by increasing the population of M2 macrophages and regulatory T cells in both the bloodstream and lymphoid organs, resulting in a reduction in the severity of the disease [10] .

How to cite this article: Ahmed SW, Ali SH. Investigating the correlations Between Substance P, Antioxidant Levels, and Metabolic Markers in Non-Obese Type 2 Diabetic Patients. J Res Pharm. 2025; 29(5): 2008-2016.

ISSN: 2630-6344

https://doi.org/10.12991/jrespharm.1765036

Antioxidants are compounds that can alleviate the consequences of oxidative stress. Endogenous antioxidants comprise of reduced glutathione and antioxidant enzymes, including catalase, superoxide dismutase, glutathione peroxidase, and reductase; while exogenous antioxidants are antioxidant vitamins such as vitamins A, C, and E [11]. Both types can help prevent the production of free radicals by either removing them or speeding up their breakdown [12]. Due to the impracticality of individually measuring various antioxidant molecules, the total antioxidant status (TAS), is considered as a measurement of a sample's overall antioxidant activity. Other names for TAS are total antioxidant activity (TAA) and total antioxidant capacity (TAC) [13].

The aim of this study is to evaluate the levels of TAS and SP in Iraqi patients with T2DM, in comparison to healthy control from the general population. Additionally, aims to assess the glycemic markers and lipid profile in both groups and investigate the potential correlations between TAS and other biomarkers.

2. RESULTS

The selected group of T2DM patients and healthy control group in this study were comparable considering their anthropometric measures (age, sex, and BMI), as illustrated. The comparison is presented in Table 1.

The study enrolled participants within the age range of 35 to 60 years in the patients' group, with a median (IQR) of [52 (13)]. While in the control group, the age range was 30 to 51 years, with a median (IQR) of [40 (7)]. Therefore, there is no considerable difference in age between the group of patients with diabetes and the control groups (P = 0.062); Table 1.

Of the 53 diabetic patients surveyed, 33 were men and 20 were women, making up 62% and 38%, respectively. Alternatively, of the 32 participants in the control group, 13 were men (41% of the total) and 19 were females (59% of the total). There was no statistically significant difference between the sexes in the two groups, as shown in Table 1.

Table 1. Characteristics of participants' demographics

Variables		Diabetes Patients n=53	Control n=32	P-Value
Age(year)		52(13)	40(7)	0.062
Gender	**Male**	33(62%)	13(41%)	0.073
	Female	20(38%)	19(59%)	
BMI(kg/m2)		26.2(4)	25.53(3)	0.068

Where n=number, BMI= body mass index
* Significant when p<0.05

Table 2 shows that individuals with T2DM have elevated fasting serum glucose (FSG) levels in comparison to the control group. The T2DM group exhibits a higher median (IQR) compared to other groups. There are substantial differences between the groups (P = 0.001). In addition, the studied groups were showed a significant difference in their fasting serum insulin levels. The glycated hemoglobin (Hb1Ac) also demonstrates a statistically significant difference in the measured value between the groups (P =0.001). According to the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) analysis, there were notable distinctions between the diabetic and control groups. Individuals with diabetes exhibit higher values (p = 0.001).

Lipid profile shows statistically significant differences in the measured values of total cholesterol (TC), triglyceride (TG) , low -density lipoprotein (LDL), and high-density lipoprotein (HDL) between the diabetes patients and the control groups (P =0.001); as the results are expressed as median (IQR) in Table 2.

Table 2. Serum levels of studied biochemical markers among Groups as median (IQR)

Variables	Diabetes Patients n=53	Control n=32	P -Value
FSG (mg/ dL)	219.13 (31.18)	90.94 (13.57)	0.001*
Insulin (µU/ml)	3.03 (1.27)	1.99 (0.381)	0.001*
HOMA-IR	1.687 (0.704)	0.446 (0.60)	0.001*
HbA1c (%)	8.10 (1.70)	5.00 (0.70)	0.001*
TG (mg/ dL)	209.48 (13.20)	139.49 (14.54)	0.001*
TC (mg/ dL)	176.50 (17.80)	138.31 (17.93)	0.001*
LDL (mg/ dL)	76.62 (19.473)	51.85 (16.59)	0.001*
HDL (mg/ dL)	52.64 (2.23)	59.14 (5.07)	0.001*
VLDL (mg/ dL)	41.89 (2.64)	27.89 (2.91)	0.001*
SP (p g/ml)	181.49 (79.93)	445.40 (136.25)	0.001*

Where n=number, FSG =Fasting Serum Insulin, HOMA-IR= Homeostatic Model Assessment-Insulin Resistance, HbA1c= Glycated hemoglobin, TC=Total Cholesterol , TG= Triglycerides, LDL=Low Density Lipoprotein, VLDL=Very Low Density Lipoprotein, HDL=High Density Lipoprotein.
* Significant when $p<0.05$

Total antioxidant status shows significant variances between the groups. The T2DM group had been subjected to the lowered values, with a median (IQR) of 71.363mmol/L (12.589) Vs. 137.844 (66.985) for the controls, as illustrated in Figure 1.

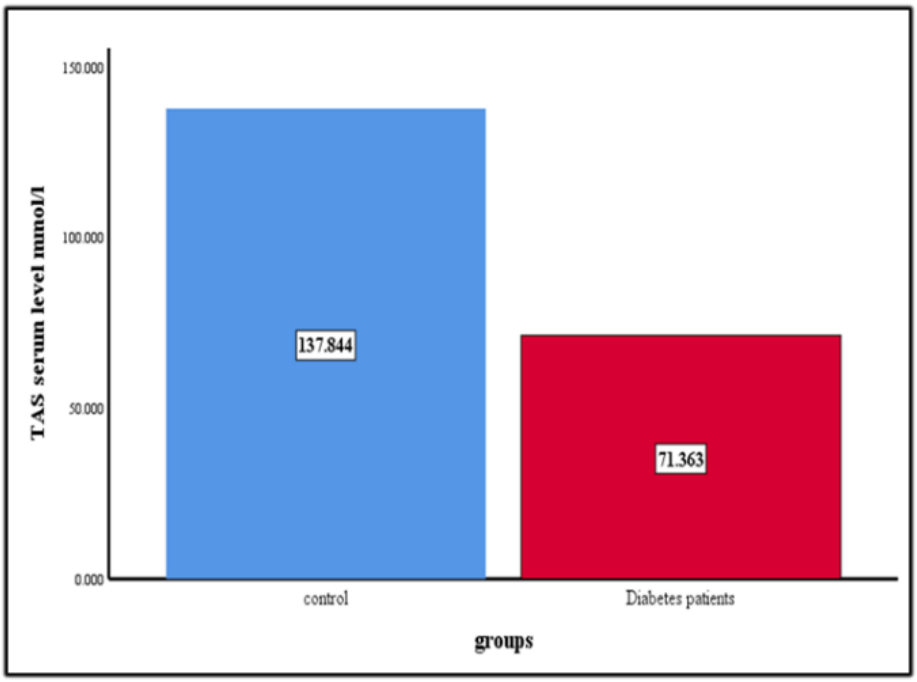

Figure 1. Serum Level of Total Antioxidant Status (TAS) in Studied Groups

The present investigation identified a statistically significant disparity in the measured serum level of SP between the groups. The T2DM group had a lower median value of 181.49 pg/ml than the control group of 445.37 pg/ml; Figure 2.

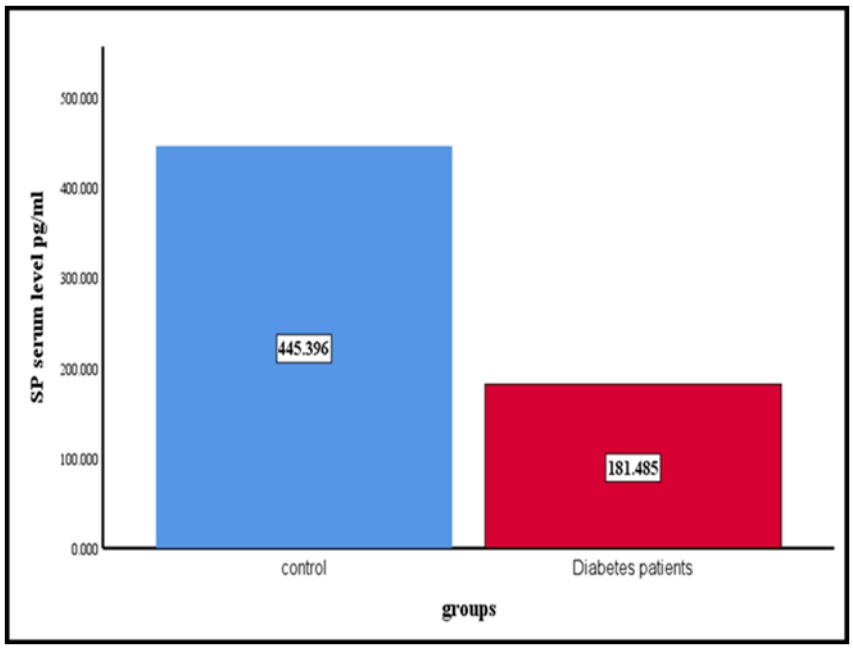

Figure 2: Serum Level of Substance P (SP) in Studied Groups

The results of correlations analysis regarding TAS and SP for diabetes patients (n=53) are displayed in Table 3.

The serum TAS showed significant negative correlations with fasting FSG and LDL, while it has shown significant positive correlations with HDL; (P<0.05). There were no significant correlations involving SP and the other variables.

Table 3. Spearman's Correlation Coefficient of Serum TAS and SP Levels with the Studied Variables in Diabetics

Variable		SP	TAS
	P-value	0.068	0.263
Age(years)	**rho**	-0.253	-0.156
BMI	**P-value**	0.769	0.985
	rho	0.041	0.003
HbA1c	**P-value**	0.959	0.165
	rho	0.007	0.193
Insulin	**P-value**	0.165	0.636
	rho	-0.194	-0.066
FSG	**P-value**	0.439	0.001
	rho	-0.109	-0.457**
HOMA-IR	**P-value**	0.176	0.161
	rho	-1.898	-0.195
TG	**P-value**	0.247	0.765
	rho	-0.162	0.042
TC	**P-value**	0.166	0.006
	rho	-0.193	0.371**
HDL	**P-value**	0.632	0.007
	rho	0.067	0.365**
LDL	**P-value**	0.257	0.006
	rho	-0.159	-0.371**
VLDL	**P-value**	0.247	0.765
	rho	-0.162	0.042

Where n=number, BMI=body mass index, FSG =Fasting Serum Insulin, HOMA-IR= Homeostatic Model Assessment-Insulin Resistance, HbA1c= Glycated hemoglobin, TC=Total Cholesterol, TG= Triglycerides, LDL=Low Density Lipoprotein, VLDL=Very Low-Density Lipoprotein, HDL=High Density Lipoprotein.
*Correlation is significant when P-value ≤ 0.05

3. DISCUSSION

In this study, the groups were carefully selected to ensure that there were no differences in age, sex, or BMI among the participants. This was done to avoid any potential influence of these factors on the biomarkers being investigated in the current study. Individuals diagnosed with diabetes exhibited elevated FSG levels compared to healthy control subjects [14–16] . In addition, the individuals with diabetes showed higher levels of fasting insulin of percentage increase of (>50%) and HOMA-IR (>250%), indicating inadequate management of the disease [17,18]. the insulin levels and HOMA-IR values in non-obese T2DM patients were not as high as expected (Table 2); These findings are consistent with the results drawn in earlier studies [19]. This is likely due to a combination of reduced insulin secretion and minimal or no insulin resistance. It has been observed that circulating insulin levels in non-obese diabetic patients are lower compared to their obese counterparts, these findings suggest a more severe beta-cell failure in the non-obese group, Importantly, this failure appears to be functional rather than structural[20].The HbA1c that used as an indicator to determine the average blood glucose level in an individual's bloodstream, as the hemoglobin becomes glycated. There is a clear association between the HbA1c values and the blood glucose levels [21].

The study revealed that the HbA1c values were significantly higher (>60%) compared to the control group. These elevated values primarily will contribute to the development of various complications associated with diabetes [22,23]. Patients with T2DM had higher lipolysis and lower glucose absorption, which led to an increase in TG production by adipose tissue [24] . This study showed that T2DM patients had elevated serum TG levels and decreased HDL levels, reflecting the presence of dyslipidemia. An increase in insulin resistance would lead to an increase in the amount of free fatty acids (FFAs) that are delivered to the liver because the uptake of FFAs by skeletal muscle and adipose tissue is mediated by insulin. This results in elevated VLDL-cholesterol concentrations and overproduction of VLDL, which is clinically characterized as hypertriglyceridemia, also reduced lipoprotein lipase activity may also lead to an accumulation of TG-rich lipoproteins in circulation [25]. Our data indicated that the diabetic group exhibited higher levels of TC, TG, and LDL, while also showing lower levels of HDL compared to healthy control. Variations in lipid metabolism are regarded as risk factors for an increased incidence of cardiovascular complications related to diabetes [26,27]. Antioxidant defenses in the body continuously defeat the natural production of oxidants, ensuring a stable redox balance and protecting against damage. Insufficient antioxidant defenses or disruptions in redox signaling can lead to cellular membrane damage and the inhibition of essential enzymes and pathways [28]. The current study is in line with Rani et al. [29] and Picchi et al. [30] that there is a significant decrease in the TAS among diabetic patients in comparison to controls. Several studies have demonstrated an increase in antioxidant activity in diabetes, which is likely a result of a compensatory response to the oxidant environment associated with diabetes [31]. The SP/NK1R system and diabetes are related as well. Significantly, deregulated expression of SP has been reported in diabetes and diabetes-associated chronic complications [32]. This study confirmed the findings by Guo et al.[33] ,Yan et al. [34] and Wang et al.[35] , that serum SP content was significantly lowered in non-obese T2DM patients as compared to healthy controls. However, a study by Fuj et al. refuted this evidence in obese diabetes patients[36].

The study findings indicate that there was no significant correlation between SP levels and the variables that were examined. However, the statistical analysis showed a negative association between SP levels and fasting insulin levels, HOMA-IR, and lipid profile (except for HDL) and had a positive association with BMI, HbA1c, and HDL, as shown in Table (3). This finding is consistent with a previous study conducted by Kunt et al. [37]. Oxidative stress is typically associated with tissue damage and inflammation, in diabetic individuals, where oxidative stress levels are often elevated, SP can exert beneficial effects by promoting neuroprotection, modulation of oxidative stress, wound healing, and regulation of inflammation as mentioned by studies [9,38] . Hyperglycemia initiates metabolic disorders by activating abnormal pathways that results in intracellular oxidative tissue stress. Oxidation of glucose and the generation of advanced glycation products are the consequence. Therefore, the rising oxidative stress is the main cause for the use of antioxidants as they are the substances which reduce the level of damage [39],in this study the serum TAS displayed significant negative correlations with FSG as confirmed with Baharirad et al [40]. Serum TAS displayed no significant correlations with HbA1c as agreed with Piechota study [41] ,and no correlation observed with HOMA-IR [42]. A positive correlation exists between HDL and TAS in diabetics group, as in an environment of oxidative stress brought on by hyperglycemia, insulin resistance, and increased plasma TGs may trigger a mechanism initiated by cholesteryl ester transfer protein that results in a generation of cholesteryl ester depleted, then

renal catabolization of small HDL occurs rapidly [43], as well negative correlation with LDL, Nour Eldin et al. [44].

4. CONCLUSION

Since TAS was absorbed more to fight free radicals caused by oxidative stress, its circulation may have been reduced. Diabetes treatments emphasize glucose uptake and lack antioxidants. Early intervention with antioxidant-rich meals, vitamins, and trace minerals is essential. Future research will examine SP's antioxidant molecular pathways, taking into account the complex connection between SP, oxidative stress, and diabetic pathogenesis. The indirect association between SP and glycemic indices' mechanisms are unknown and need further investigation. However, the considerable decrease in SP levels raises questions about its function in diabetes pathogenesis, comorbidities, and cardiovascular health.

5. MATERIALS AND METHODS

5.1. Study design

A case-control study design was conducted at The National Center of Diabetes/ College of Medicine / Mustansiriyah University, Baghdad; from October/ 2023 to January/ 2024, using. The study included **Group 1:** fifty-three T2DM, from 35 to 60 years of age, under the supervision of a specialized endocrinologist. Of these patients, 33 were males and 20 were females. **Group 2:** The control subjects matched the corresponding patients (age, sex, and BMI), consisting of a total number of thirty-two healthy individuals (13 male and 19 female), selected from the general community, with ages ranging from 30 to 51 years.

5.2. Inclusion criteria

Diabetic patients aged 18 years old or more who diagnosed with T2DM for at least one year and had a BMI ranging (18.6 to 29.9 kg/m²). These patients were exclusively on oral hypoglycemic medications and had never been treated with insulin.

5.3. Exclusion criteria

Alcoholic patients, those with autoimmune disease, chronic inflammation, chronic kidney, and liver diseases, malignant diseases, pregnant or lactating women, or having other endocrinopathies, patients with dyslipidemia or on statin therapy. Also, patients with type 1 diabetes were excluded.

5.4. Ethical consideration

The research protocol was granted approval from the College of Pharmacy Scientific and Ethical Committee / University of Baghdad (No. RECAUBCP6102023K). Additionally, informed agreement was obtained from each participant in the study.

5.5. Materials

Five milliliters of fasting venous blood were collected from the participants and collected in a gel tube; the samples were subjected to centrifugation at 4000 rpm for a duration of 15 minutes. The serum was stored in a 1.5 milliliter Eppendorf tube and stored in a refrigerator at a temperature of -20°C for later measurement of the study biomarkers. Serum insulin, SP, and TAS were measured by ELISA kits provided by Cloud-clone Corp.(CCC, USA), and HbA1c was measured by boronate affinity assay using the Nyco-Card Reader II(Sweden), The colorimetric test was used to evaluate FSG, TC, TG, HDL levels using the corresponding kits from Linear chemicals (Spain), LDL, as estimated by the Friedewald formula in (mg/dl) which is TC minus HDL minus TG divided by 5 , Insulin resistance can be predicted using HOMA-IR, which is a simplified by the formula of multiplying the fasting insulin (µU/ml) by the fasting glucose (mg/dl) and dividing the result by 405 [45].

5.6. Statistical analysis

The statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS) (Windows version 26). The Shapiro-Wilk test was used to evaluate the normality of the data distribution, The obtained P-values for the measured data were found to be less than 0.05, indicating that the data did not follow a normal distribution. Consequently, non-parametric tests were employed for data analysis. Using the Mann

-Whitney U test, we compared the patient and control groups' outcomes; The results are expressed as median (IQR). Statistical analysis revealed that the differences were significant at the $p < 0.05$ level. Categorical variables were expressed as numbers and percentages and differences were expressed using the Chi-Squared test. Parameter correlations were examined using Spearman's correlation test [46,47].

6. LIMITATIONS

A small sample size of 85 participants may have implications for the generalizability and robustness of the study findings and it is exclusive in a single diabetic center as the sole location of data collection, which may not fully represent the diversity of experiences.

7. RECOMMENDATIONS

1-Involving many centers will provide a diversified patient pool, reduce biases, and improve study efficacy.
2-individuals' criteria: a diverse range of BMIs to analyze marker levels in both obese and non-obese individuals for a more thorough investigation.
3- Examine connections between SP and additional biomarkers to provide insight into illness development, increase data for biomarker correlations, and enhance study conclusions.
4- to try vitamin D and E treatments to modulate the condition [48].

8. ABBREVIATIONS

SP= Substance P.
TAS= total antioxidant status.
T2DM= type 2 diabetes mellitus.
BMI=body mass index.
FSG =Fasting Serum Insulin.
HOMA-IR Homeostatic Model Assessment-Insulin Resistance.
HbA1c= Glycated hemoglobin.
TC=Total Cholesterol.
TG= Triglycerides.
LDL=Low-Density Lipoprotein.
VLDL=Very Low-Density Lipoprotein.
HDL=High-Density Lipoprotein

Author contributions: Concept – S.H.A.; Design – S.W.A., S.H.A.; Supervision – S.H.A.; Resources – S.W.A.; Materials – S.W.A.; Data Collection and/or Processing – S.W.A.; Analysis and/or Interpretation – S.W.A., S.H.A.; Literature Search – – S.W.A., S.H.A.; Writing – S.W.A.; Critical Reviews – S.H.A.

Conflict of interest statement: The authors declared no conflict of interest" in the manuscript.

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