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Original article

Relationship between Serum Sialic Acid Level and Diabetic Neuropathy in Egyptian Patients with Type 2 Diabetes Mellitus

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Abstract

Background: Diabetic neuropathy, a serious microvascular consequence of diabetes mellitus (DM), affects up to 50% of those with type 1 and type 2 DM. It is the most typical DM complication. A person with diabetes is stated to have diabetic peripheral neuropathy once all other potential causes of peripheral nerve damage have been ruled out**.** This study's objective was to measure the serum sialic acid concentration in patients with type 2 DM and to assess if it could be used as an early marker of diabetic neuropathy **Methods:** This was a cross sectional study that was carried out on 40 patients subdivided into 3 groups. The first group involved 25 patients with diabetic neuropathy, second group involved 15 patients without diabetic neuropathy and the third group involved 10 healthy patients serving as a control group. All patients were selected from those attending the outpatient diabetic clinic at Benha University Hospital between July 2017 and July 2018. **Results:** when comparing diabetic neuropathy patients to the control group of individuals, it was discovered that the serum sialic level was higher in diabetic patients with neuropathy than in diabetic patients without neuropathy. The age of diabetes diagnosis or the duration of diabetes were not related to serum sialic acid levels. **Conclusions:** serum sialic acid level is significantly increased in patients with diabetic neuropathy, and it is positively correlated with the glycemic control parameters.

Keywords: Diabetes Mellitus, Diabetic Neuropathy, Sialic Acid

Introduction

Diabetes mellitus (DM) is a metabolic condition of the metabolism of carbohydrates that results in hyperglycemia and a secondary disturbance of the metabolism of proteins and lipids. According to experimental data, a number of molecular pathways may contribute to the emergence of both microvascular and macrovascular problems in diabetic people (1).

Up to 50% of diabetics may get diabetic neuropathy, as a significant consequence of the disease. But with constant blood sugar control and a healthy lifestyle, you may frequently prevent diabetic neuropathy or reduce its progression (1).

DM was connected to the activation of the innate immune response due to elevated levels of acute-phase reactants such C-reactive protein (CRP) and sialic acid, which have been proposed to be predictors of the risk of developing type 2 DM. The term "sialic acid" describes a group of derivatives of neuraminic acid, an acidic sugar with a nine-carbon backbone. This name is also used for the most common member of this group, N-acetyl neuraminic acid (2).

Sialic acids (SA), the majority of which are found in glycoproteins and gangliosides; they are widely distributed in mammalian tissues and to a lesser extent in those of other organisms, such as fungi, yeasts, and bacteria (they occur at the end of sugar chains connected to the surfaces of cells and soluble proteins). That is because it appears to have developed relatively recently. However, it has been seen in certain bacterial strains' capsular polysaccharides, Drosophila embryos, and other insects. Typically, sialic acids are neither present nor visible in plants. More than half of all sialic acids come from acute-phase proteins (3).

Why diabetic people have higher amounts of SSA? May be due to the high level of serum acute-phase proteins, which are known to be present in both type 1 and type 2 DM. The defects of the red blood cell membrane, which caused the release of SA, were also found to contribute to higher SSA levels in diabetic patients. Inflammatory indicators have been linked to the development of adult diabetes., supporting the idea that diabetes etiology involves an inflammatory component (4).

Additionally, it was found that serum SA levels and metabolic control were related (as estimated by HbA1C). SA and HbA1C are related, most likely due to the association between SA and microvascular issues, which are known to be associated with glycemic control and the length of diabetes (5).

In conclusion, SSA concentrations have been observed to significantly correlate with both type 2 diabetes patients and cardiovascular risk factors. Additionally, diabetic microangiopathy formation or progression is closely correlated with SA and/or other indicators and mediators of the acute-phase response (such as proinflammatory cytokines) (6).

This study aimed to measure the serum sialic acid concentration in patients with type 2 DM and to assess if it could be used as an early marker of diabetic neuropathy.

Patients and Methods

This cross-sectional study was conducted on 50 patients who were divided into three groups: the control group, which consisted of 10 healthy individuals, the second group, which contained 15 patients without diabetic neuropathy, and the third group, which contained 25 patients with diabetic neuropathy.

All patients were recruited from those who attended the outpatient diabetic clinic at the Benha University Hospital between July 2016 and July 2017. All participants in the study were informed, and written consents were obtained.

This work was authorized by the Benha Faculty of Medicine's ethical review board (Ms.5.6.2016).

Inclusion criteria were type 2 diabetic patients and type 2 diabetic patients with neuropathy.

Exclusion criteria were type1 DM, liver cirrhotic patients, any endocrinological disorders, alcohol intake, pregnancy, malignancy or any acute and chronic inflammatory disorders.

Age, sex, body mass index (BMI), unique behaviors, features of their sickness (age of onset, symptoms, medications, complications), co-existing ailments, and comorbidities are just a few of the demographic and clinical data that will be gathered (Hypertension, ischemic heart diseases, chronic kidney diseases, chronic liver diseases, and any other endocrinological disorders).

Risk factors questionnaire: They include socioeconomic characteristics and family history as home sanitation and health care domain. Biological factors: as early or late complications such as pancreatic tumors, multi-endocrine syndromes, and other CNS complications.

The following investigations were performed on every patient: fasting plasma, glucose and 2hr postprandial plasma glucose level, hemoglobin A1C, Complete blood count, Complete metabolic panel (electrolytes and liver function panel), Vitamin B-12 and folate levels, Thyroid test function, Erythrocyte sedimentation rate and C-reactive protein.

This work has been carried out by The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis:

Statistical analysis was performed using the SPSS (Statistical Package for the Social Sciences) version 28(IBM Inc., Armonk, NY, USA).
Shapiro-Wilks normality test and histograms were used to test the distribution of quantitative variables to select accordingly the type of statistical testing: parametric or nonparametric. Parametric variables (e.g., age) were expressed as mean and standard deviation (SD) and were compared using F test among the three groups with post hoc (Tukey) test to compare each two groups. Comparison between two variables within the same group was compared by paired T test. Categorial variables (e.g., sex) were expressed as frequency and percentage and were statistically analysed by Chi-square test. Evaluation of Diagnostic Performance was performed using diagnostic sensitivity, specificity, PPV and NPV. Receiver Operating Characteristic curve (ROC-curve) analysis: The overall diagnostic performance of each test was assessed by ROC curve analysis, a curve that extends from the lower left corner to the upper left corner then to

the upper right corner is considered a perfect test. The area under the curve (AUC) evaluates the overall test performance (where the area under the curve >50% denotes acceptable performance and area about 100% is the best performance for the test). A two-tailed *p* value < 0.05 was considered statistically significant.

Results

Based on the data provided, it appears that there is a statistically significant difference in the mean BMI between group 1 and group 2 with a *p*-value of 0.008. Group 1, 2 and control had mean BMI of 28.5 kg/m2, 27.2 kg/m2 and 25.92 kg/m2 respectively. Control group had a significantly lower values than the two experimental groups. However, there were no statistically significant differences in age and sex between the three groups, as indicated by the *p*-values of 0.259 and 0.493, respectively as shown in **table 1**.

8(32%) were smokers in group 1, 4(26.6%) were smokers in group 2 and 1(10%) were smokers in control group. 15(60%) were hypertensive in group 1, 11(73.33%) were hypertensive in group 2, and 4(40%) were hypertensive in the control group. 21(84%) had thyroid disease in group I, and 10(66.5%) patients in group 2. Non the participants in the control group had an endocrine disease. There was an insignificant difference among the three groups as regards smoking, HTN, IHD, and thyroid disease (**Table 2)**.

Group 1 consisted of 25 patients, with a mean age of onset of 46±6.77 years and a mean duration of 16.53±8.52 years. Most of them were treated with oral medication (64%). Group 2 consisted of 15 patients, with a mean age of onset of 42.87±12.69 years and a mean duration of 9.4±5.04 years. Most of them were treated with insulin (73.33%). The results of the study showed a statistically significant difference between the groups in terms of the duration of DM (*p*-value < 0.05). However, there was no significant difference between the groups in terms of age of onset or type of treatment (*p*-value > 0.05) (**Table, 3)**.

Table 4 demonstrates significant differences between the three groups in terms of fasting blood sugar (FBS), postprandial blood sugar (PPBS) and glycosylated haemoglobin (HbA1c) levels. Group 1 had the highest levels of FBS (174.2±24.22 mg/dl), PPBS (257.12±65.07 mg/dl) and HbA1c (8.7±0.92 %), while the control group had the lowest levels of FBS (93.1±21.18 mg/dl), PPBS (128.3±53.21 mg/dl) and HbA1c (5.68±0.45 %). The differences between the groups were all statistically significant ($p < 0.001$). These results indicate that group 1 has the highest levels of FBS, PPBS and HbA1c levels than group 2 and the control group, suggesting an increased risk of diabetes and other metabolic disorders.

Table 5 provides a comparison of the cholesterol, triglyceride, ALT (alanine transaminase), AST (aspartate aminotransferase), and TSH (thyroid stimulating hormone) levels among three different groups. The results show that the mean cholesterol level was 188.24 mg/dl in group 1, 187.73 mg/dl in group 2, and 189 mg/dl in the control group with a statistically significant difference between

the studied groups (p<0.001). The range for cholesterol was 150-240 mg/dl in all three groups. The mean triglyceride level was 147.48 mg/dl in group 1, 142.27 mg/dl in group 2, and 112.5 mg/dl in the control group with a statistically significant difference between the studied groups (p<0.001). The range for triglycerides was 110-189 mg/dl in group 1, 110-187 mg/dl in group 2, and 91-132 mg/dl in the control group. The mean ALT level was 29 U/L in group 1, 30.13 U/L in group 2, and 27.3 U/L in the control group with insignificant difference between the three groups (p= 0.723). The range for ALT was 15-45 U/L in all three groups. The mean AST level was 26.88 U/L in group 1, 27.6 U/L in group 2, and 25.8 U/L in the control group with insignificant difference between the three groups (p= 0.835). The range for AST was 17-40 U/L in all three groups. Finally, the mean TSH level was 3.28 mIU/L in group 1, 3.9 mIU/L in group 2, and 2.36 mIU/L in the control group. with insignificant difference between the three groups (p= 0.232).

There was a significant difference among the studied groups as regards Sialic acid levels. The sialic acid level was significantly higher in group 1 compared to both group 2 and the control group and was significantly higher in group 2 compared to the control group as shown in **table 6.**

Sialic acid is a significant predictor for diabetic neuropathy at a cutoff point >61.25 with a strong AUC =0.881 with a sensitivity of 92%, specificity of 60%, PPV of 69.7%, NPV of 88.2% (**Figure, 1).**

Table 1: Demographics of the studied groups

		Group 1 (n=25)	Group 2 (n=15)	Control group (n=10)	*p* value
Age (years)	**Mean ± S.D.**	55.4±7.72	59.4±9.6	58.8±5.83	0.259
	Range	42-71	40-75	52-68	
Sex	**Male**	8(32%)	4(26.67%)	1(10%)	0.493
	Female	17(68%)	11(73.33%)	9(90%)	
BMI (kg/m^2)	**Mean ± S.D.**	28.5±2.46	27.2±2.21	25.92±2.04	*p*1=0.07
	Range	23-32	24-32	23-30	0.008* *p* 2=0.003 *p* 3=0.18

BMI= body mass index; S.D.= Standard deviation; *= Significant as p value <0.05; p1= p value between group 1 and group 2; p2= p value between group 1 and group 3; p3= p value between group2 and control group.

Table 2: Comorbidities among the studied groups

Comorbidities among the studied groups	Group 1 (n=25)	Group 2 (n=15)	Control group (n=10)	*p* value
Smoking	8 (32%)	4 (26.6%)	1 (10%)	0.799
HTN	15 (60%)	11 (73.33%)	4 (40%)	0.253
IHD	15 (60%)	15 (100%)	0 (0%)	----
Thyroid disease	21 (84%)	10 (66.5%)	0 (0%)	0.203

IHD= Ischemic heart disease; HTN= hypertension; p value >0.05= statistically insignificant

Table 3: History of DM among the studied groups

		Group 1 (n=25)	Group 2 (n=15)	Control group (n=10)	*p* value
Age of onset of DM (years)	**Mean ± S.D.**	46±6.77	42.87±12.69	----	0.313
	Range	36-60	25-70	----	
Duration of DM (years)	**Mean ± S.D.**	16.53±8.52	9.4±5.04	----	0.001*
	Range	3-20	5-40	----	
Treatment of DM	**Oral**	16(64%)	4(26.67%)	0(0%)	0.418
	Insulin	9(36%)	11(73.33%)	0(0%)	

DM= Diabetes mellitus; S.D.= Standard deviation; *= statistically significant as p value <0.05

Table 4: Laboratory findings among the studied groups.

		Group 1 (n=25)	Group 2 (n=15)	Control group (n=10)	*p*value
FBS (mg/dl)	**Mean ± S.D.**	174.2±24.22	140.33±34.68	93.1±21.18	<0.001*
		***p* 1=0.001, *p* 2<0.001, *p* 3:0.050**			
PPBS	**Mean ± S.D.**	257.12±65.07	249.07±78.08	128.3±53.21	<0.001*
HbA1c(%)	**Mean ± S.D.**	8.7±0.92	8.15±0.61	5.68±0.45	<0.001*
		***p* 1 =0.041, *p* 2<0.001, *p* 3<0.001**			

SD = Standard deviation, FBS = fasting blood sugar, PPBS = postprandial blood sugar, *= Significant as ***p*** value <0.05; ***p***1= ***p*** value between group 1 and group 2; ***p***2= ***p*** value between group 1 and group 3; ***p***3= ***p*** value between group2 and control group.

Table 5: Lipid profile and liver function test among the studied groups

		Group 1 (n=25)	Group 2 (n=15)	Control group (n=5)	*p* value
Cholesterol(mg/dl)	**Mean ± S.D.**	188.24±25.45	187.73±24.26	189±28.46	<0.001*
	Range	150-240	155-240	150-240	
TG (mg/dl)	**Mean ± S.D.**	147.48±27.48	142.27±28.27	112.5±14.56	<0.001*
	Range	110-189	110-187	91-132	
ALT(U/L)	**Mean ± S.D.**	29±8.56	30.13±7.6	27.3±10.01	0.723
	Range	15-45	19-45	15-40	
AST (U/L)	**Mean ± S.D.**	26.88±7.3	27.6±7.63	25.8±7.02	0.835
	Range	17-40	19-40	17-40	
TSH (mIU/L)	**Mean ± S.D.**	3.28±2.22	3.9±2.71	2.36±0.46	0.232
	Range	1.26-10.8	1.26-10.8	1.77-3	

TG= Triglycerides,; ALT= Alanine transaminase; AST= Aspartate aminotransferase; TSH= thyroid stimulating hormone; S.D.= Standard deviation; *= significant as p-value < 0.05.

Table 6: sialic acid level among the studied groups

		Group 1 (n=25)	Group 2 (n=15)	Control group (n=5)	*p*value
Sialic acid level (mg/dl)	**Mean ± S.D.**	75.9±14.58	63.59±5.39	51.78±5.7	<0.001
	Range	42.5-121	53.5-73.5	44-59.5	
		***p*1<0.001, *p*2<0.001, *p*3<0.001**			

S.D.= Standard deviation ; *= Significant as ***p*** value <0.05; ***p***1= ***p*** value between group 1 and group 2; ***p***2= ***p*** value between group 1 and group 3; ***p***3= ***p*** value between group2 and control group.

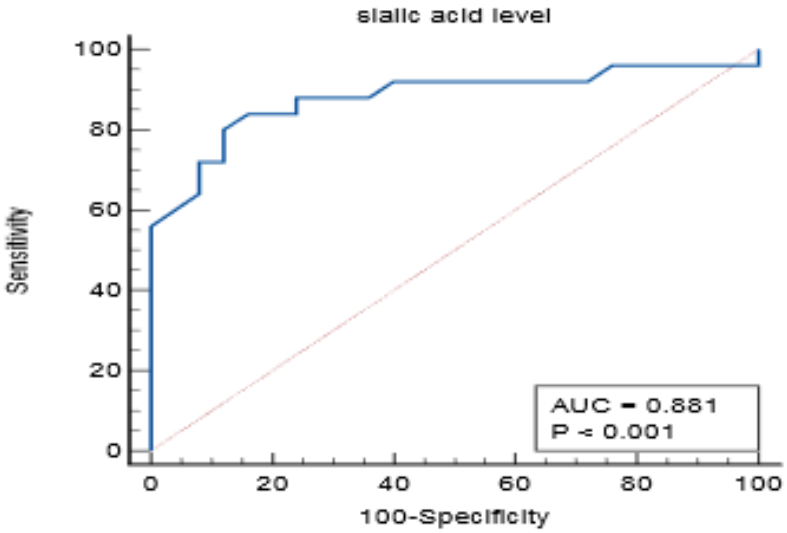

Fig. 1: Diagnostic accuracy of Sialic acid in prediction of diabetic neuropathy.

Discussion

In this study, sialic acid levels were found to be positively correlated with fasting blood glucose, postprandial blood glucose, and HbA1C. These parameters were identified as predictors of serum sialic acid level. The study revealed that sialic acid levels were significantly higher in the diabetic group compared to the control group, and this difference was found to be statistically significant (7).

Subzwari and Qureshi found (8) that subjects with diabetes had a significantly higher level of serum sialic acid. Sialic acid concentrations in the blood and urine were higher in people with diabetes than in the general population, particularly in type 2 diabetes patients.

It has been discovered that diabetes without complications, particularly microvascular ones, has significantly higher serum sialic acid levels than controls. When diabetics without problems were compared to healthy controls, Poddar and Ray found a definite rise in serum sialic acid levels (9).

Serum sialic acid levels in this investigation were positively correlated with BMI, cholesterol, and TGs. This was in line with the findings of Englyst et al., who discovered that the total body fat had an impact on the fasting sialic acid level and is used as a predictor of it. When comparing diabetes patients with the control group, we discovered that if body fat is similar to serum sialic acid concentration, the serum sialic acid concentration is higher (10).

Sialic acid, a vital blood component, is elevated in diseases like diabetes and several types of cancer. Since diabetes mellitus (DM), which is linked to an increase in SA concentration along with other difficulties, is also connected with this relationship, our current study was done to assess the relationship between serum SA and type 2 diabetes. Given the connection between SSA and diabetic issues, particularly microvascular effects, we are also concentrating on neuropathy (11).

The vast majority of postclassical states where tissue death, proliferation, depolymerization, or inflammation are the underlying pathologies have been shown to have unusually high SA concentrations in the human serum. Sialic acid is the terminal component found at the non-reducing end of the carbohydrate chains of glycoproteins and glycolipids (12).

It is unclear how exactly type 2 diabetes produces atherosclerotic vascular disease. The focus is moving away from citing risk factors like insulin resistance and toward a knowledge of the mechanism happening at the vasculature (13). Patients with non-insulin-dependent diabetes may have an increased risk of cardiovascular disease due to an increase in the levels of serum sialic acid (14).

One of the acute phase reactions is thought to be the presence of sialic acid in the blood. SSA levels were higher in type 2 diabetes than in healthy control participants. The outcomes were contrasted with findings

from related investigations. In participants with type 2 diabetes, Yilmaz et al. (15) discovered considerably higher levels of SSA and the reactive compounds to barbituric acid. Additionally, Ekin et al. and Abdella et al. observed that diabetics' SA levels were higher than those of controls.

It has been demonstrated that serum or plasma sialic acid levels and microvascular complications in type 2 diabetes mellitus are connected. An association with neuropathy has not yet been observed, unless associations between sialic acid and risk factors for vascular illnesses such lipids, smoking, hyperfibrinogenemia, and lipoprotein have also been demonstrated (16).

The liver produces acute-phase glycoproteins, which are then activated by proinflammatory cytokines such as interleukin-6, interleukin-1, and tumor neurosis-alpha. Sialic acid is a component of the oligosaccharides side chain. A marker of the acute-phase reactant response is plasma sialic acid (17).

For instance, data demonstrating that proinflammatory cytokines contribute to microangiopathy by encouraging dyslipidemia, which in turn causes endothelial dysfunction by increasing capillary permeability and causing prothrombotic properties as well as promoting leukocyte recruitment by synthesizing adhesion molecules and chemoattractant, support the latter (18).

Therefore, it is doubtful that the decor alienation of cellular components and lipoprotein particles led to a rise in the amount of sialic acid in the blood. However, there is evidence that sialic acid is decreased in the endothelium in conditions including atherosclerosis, LDL, and diabetes, which may have pathophysiological implications for developing a vascular disease (19).

Another finding is that there is a sex difference in type 2 diabetes, with women having significantly greater plasma sialic acid concentrations than males. Serum sialic acid levels in non-diabetic patients do not differ by gender. Uncertainty surrounds the relevance of this gender gap, but one theory suggests that diabetic women may exhibit a higher acute-phase response because they no longer enjoy the same cardiovascular disease protection as non-diabetic women. Although baseline characteristics and issue prevalence were similar between the sexes, there was a significant relationship between elevated plasma sialic acid concentrations and a variety of outcomes (retinopathy, neuropathy, and hypertension) in men but not in women (20).

Conclusion

We found a significant association between plasma sialic acid levels and microvascular complications in type 2 diabetes patients. It is therefore necessary to prospectively investigate the relationship between sialic acid and/or other markers and mediators of the acute-phase response in the development or progression of diabetic microangiopathy (for example, proinflammatory cytokines). These studies may identify biomarkers for those who are more likely to have tissue issues. Further studies should be conducted

to investigate the underlying causes of these differences and to assess potential interventions for reducing the risk of diabetes in this population.

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