Original Article

Relationship between Serum Sialic Acid Concentration and Diabetic Nephropathy in Egyptian Patients with Type 2 Diabetes Mellitus

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Abstract

Aim: Diabetic nephropathy is a major microvascular complication of diabetes mellitus (DM), and it is the most common cause of end-stage renal disease worldwide. Sialic acid is considered as an acute-phase reactant. Serum sialic acid level was found to be increased in diabetic nephropathy patients. We 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 nephropathy. **Subjects and Methods:** This was a cross-sectional study that was carried out on 40 patients subdivided into 3 groups, first group involved 25 patients with diabetic nephropathy, second group involved 15 patients without diabetic nephropathy and the third group involved 10 patients serving as control group. All patients were selected from those attending the outpatient diabetic clinic at Benha University Hospital between July 2017 and July 2018. Mean and standard deviation (±SD) were used for quantitative data, and *t* test, Fisher extract test, and regression analysis were used for statistical analysis. A *P* value <0.05 was considered statistically significant, whereas >0.05 statistically insignificant. **Results:** On comparing patients with diabetic nephropathy with the control group patients we found that serum sialic level is increased and this was statistically significant and also in diabetic patients with nephropathy when compared to diabetic patients without nephropathy. The age of the onset of the discovery of diabetes and the duration of diabetes had no impact on serum sialic acid level. **Conclusion:** This study showed that serum sialic acid level is significantly increased in patients with diabetic nephropathy, and it is positively correlated with the glycemic control parameters and negatively correlated with estimated glomerular filtration rate, and it could be used as an early predictor of albuminuria and decrease of creatinine clearance.

Keywords: Diabetic nephropathy, sialic acid, type 2 diabetes mellitus

Introduction

Diabetes mellitus (DM) is a metabolic disorder of carbohydrate metabolism leading to hyperglycemia with secondary disturbance of protein and lipid metabolism.[1] Experimental evidence suggests that several molecular pathways may be implicated in the development of diabetic kidney disease.[2] Diabetic nephropathy (DN) is characterized by a progressive increase in the excretion of protein, particularly albumin, an early and continuing rise in blood pressure, and a late decline in glomerular filtration rate (GFR), leading eventually to end-stage renal disease (ESRD).[3] DM was associated with activation of innate immune response with increased levels of acute phase reactant, such as C-reactive protein (CRP) and sialic acid, have been proposed to be predictors of the risk of developing type 2 DM.[4] Sialic acid is a generic term for a family of derivatives of neuraminic acid, an acidic sugar with a nine-carbon backbone. It is also the name for the most common member of this group, N-acetylneuraminic acid. Sialic acids are found widely distributed in animal tissues and to a lesser extent in other organisms, ranging

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from fungi to yeasts and bacteria, mostly in glycoproteins and gangliosides (they occur at the end of sugar chains connected to the surfaces of cells and soluble proteins) That is because it seems to have appeared late in evolution. However, it has been observed in Drosophila embryos and other insects and in the capsular polysaccharides of certain strains of bacteria.[3] Generally, plants do not contain or display sialic acids.[5] Acute-phase proteins account for more than 50% of the total sialic acid. Free sialic acid and creatinine are handled by the kidneys in the same way, being dependant on glomerular filtration and no tubular reabsorption, total sialic acid is elevated in renal disease, diabetes, variety of central nervous system disorders, ovarian cancer, and arthritis.[6] Diabetes patients with albuminuria whatever its type were associated with increased level of serum sialic acid.[7] In DN, there is a greater increase in sialic acid due to the damage of the vascular endothelial cells, and it is considered as a newly established potential risk factor for the development of DN.[8]

Subjects and Methods

This is a cross-sectional study out on 40 patients subdivided into three groups, first group involved 25 patients with diabetic nephropathy, second group involved 15 patients without diabetic nephropathy and the third group involved 10 patients serving as control group. All patients were selected from those attending the outpatient diabetic clinic at Benha University Hospital between July 2017 and July 2018. All subjects were informed about the study, and written consent was obtained. This study was approved by the ethical committee in Benha Faculty of Medicine.

Study design

Thorough history and clinical examination were performed on every patient with special stress on age, sex, body mass index (BMI), smoking state, type and duration of diabetes, medications, especially metformin and pioglitazone as it affects serum sialic acid level, complications, and other comorbidities; and laboratory tests were carried out on every subject as fasting and postprandial plasma glucose level (mg/dL), cholesterol measured by liquid chromatography and enzymatic assay (mg/dL), triglycerides (TG), glycated hemoglobin (HbA1c) measured by immunoassay and enzymatic assay, serum creatinine (mg/dL), blood urea (mg/dL), estimated GFR using Cockcroft–Gault formula (mL/min/1.73 m^2) (the Cockcroft–Gault formula[9] is as follows: CCr = {[(140–age) × weight]/(72 × SCr)} × 0.85 [if female]), 24-h urinary albumin by 24-h collection (g/day), and serum sialic acid level (ug/mL). The kit measures free sialic acid but bounded form is measured by carrying out a hydrolysis procedure as follows: the sample is dissolved in a final concentration of 2 M acetic acid and heated to 80°C to release sialic acid.

Statistical analysis

Data management and statistical analysis were done using SPSS version 25 (IBM, Armonk, NY, USA).

Numerical data was summarized as means and standard deviations for quantitative data and frequency and distribution for qualitative data.

Analytical statistics: Categorical data was summarized as numbers and percentages.

ANOVA. Different parameters were compared using (F value): used to compare mean of more than two groups of quantitative data.

Inter-group comparison of categorical data was performed by using fisher exact test (FET).

Correlation analysis was done using Spearman's correlation. "r" is the correlation coefficient.

It ranges from -1 to +1. -1 indicates perfect negative correlation, +1 indicates perfect positive correlation and 0 indicates no correlation.

All *P* values were two sided. P values less than 0.05 were considered significant.

Results

The age of the studied groups ranged from 45 to 82 years with the mean age of 58 years, of which 16 were males (32%) and 34 were females (68%), and BMI ranged from 22 to 47 kg/m^2 with the mean BMI of 30.2 kg/m^2. This study showed that BMI was significantly high in group A compared to group B and C [Table 1].

Table 1: Demographic characteristics in different study groups

Items	Groups						*F* test	*P* value
	Group A		Group B		Group C			
	Patients with diabetic nephropathy (*n* = 25)		Patients without nephropathy (*n* = 15)		Control (*n* = 10) healthy volunteers			
Age (years)	10.64 ± 60.04		57.47 ± 7.66		55.8 ± 5.9		0.901	NS
BMI (kg/m^2)	32.36 ± 6.49		30.13 ± 5.24		25.20 ± 1.39		6.087	HS
Sex	%	*N*	%	*N*	%	*N*	Total *N* = 50	Total %
Female	76	19	66.7	10	50	5	34	68
Male	24	6	33.3	5	50	5	16	32

BMI = body mass index, NS = non-significant, HS = highly significant

There was a significant increase in fasting plasma glucose (FPG), postprandial blood glucose (PPBG), HbA1c, serum cholesterol, serum triglycerides, serum creatinine, blood urea, 24-h urinary albumin, and sialic acid level in group A (patients with DN) compared to group B and C (patients without nephropathy and control, respectively), and a significant decrease in estimated GFR in group A patients compared to group B and C [Table 2].

There was a significant increase in FPG, PPBG, HbA1c, cholesterol, triglycerides, creatinine, urea, 24-h urinary albumin, estimated GFR (e-GFR), and sialic acid level in patients with DN compared to control group [Table 2].

There was a significant increase in FPG, PPBG, HbA1c, serum cholesterol, serum triglycerides, and sialic acid level in group B patients compared to group C, and a nonsignificant difference was observed in serum creatinine, blood urea, 24-h urinary albumin, and e-GFR between group B and group C [Table 2].

Also, no significant difference was observed in FPG, PPBG, HbA1c between group A and group B, and a significant increase was observed in serum creatinine, blood urea, 24-h urinary albumin, e-GFR, serum cholesterol, serum triglycerides, and the sialic acid level in group A patients compared to group B [Table 2].

Table 3 showed that there was no significant difference in the age of patients at the onset of the discovery of DM; duration of DM between group A and group B also showed that 14 patients with DN were on oral hypoglycemic and 11 patients were on insulin therapy, whereas 13 patients without DN were on oral hypoglycemic and two patients were on insulin therapy.

Correlation study as shown in Table 4 revealed a significant positive correlation between serum sialic acid and FPG, PPBG, HbA1c, BMI, serum creatinine, blood urea, urinary albuminuria, triglycerides, and cholesterol in the diabetic nephropathic group, and a significant negative correlation with estimated GFR; it also showed

Table 2: Comparison of different laboratory variables between the study groups

Items	Groups			*F* test	*P* value
	Group A, Patient with diabetic nephropathy ($n = 25$) (mean ± SD)	Group B, Patients without nephropathy ($n = 15$) (mean ± SD)	Group C, Control ($n = 10$) (mean ± SD)		
FPG (mg/dL)	190.28 ± 88.77	138.13 ± 58.82	84.40 ± 7.55	8.40	HS
PPBG (mg/dL)	235.88 ± 81.03	211.8 ± 59.59	9.37 ±123.40	10.28	HS
HbA1c (%)	7.66 ± 1.86	7.59 ± 1.41	4.8 ± 0.32	13.560	HS
Serum cholesterol (mg/dL)	219.4 ± 55.6	185.7 ± 37.6	96.5 ± 9.7	26.7	HS
Serum triglycerides (mg/dL)	238.1 ± 155.9	147.5 ± 46.8	88.5 ± 8.8	7.03	HS
Serum creatinine (mg/dL)	3.38 ± 3.04	0.79 ± 0.16	0.60 ± 0.08	9.41	HS
Blood urea (mg/dL)	106.64± 70.94	32.27 ± 7.07	29.5 ± 4.97	12.69	HS
24-h urinary albumin (g/day)	2.45 ±2.71	0.03 ± 0.02	0.03 ± 0.01	9.7	HS
e-GFR mL/min/1.73 m^2	44.4 ± 37.8	151.9 ± 32.6	45.9±177.8	61.3	HS
Sialic acid level (ug/mL)	295.06 ± 93.7	73.3±7.7	31.0 ± 5.7	80.2	HS

SD = standard deviation, DM = diabetes mellitus, FPG = fasting plasma glucose, PPBG = postprandial blood glucose, HbA1c = glycated hemoglobin, e-GFR = estimated glomerular filtration rate, HS = highly significant

Table 3: Comparison of age of patients at the onset of the discovery of diabetes mellitus, duration of diabetes mellitus, and type of treatment between group A and B

Items	Groups				*t test*	*P* value
	Group A Patient with diabetic nephropathy ($n = 25$) (mean ± SD)		Group B Patient without diabetic nephropathy ($n = 1$) (mean ± SD)			
Age of patient at the onset of the discovery of DM (years)	48.76 ± 12.6		44.73 ± 7.74		1.11	NS
Duration of DM (years)	11.28 ± 8.48		12.8 ± 6.47		0.59	NS
Type of treatment	*N.*	%	*N.*	%	Total	%
Oral hypoglycemic	14	56	14	86.7	27	67.5
Insulin	11	44	2	13.3	13	32.5

SD = standard deviation, DM = diabetes mellitus, NS = non-significant

Table 4: Correlation between serum sialic acid and different laboratory variables in diabetic nephropathic group

Categories	Pearson correlation coefficients (*r*)	*P* value
Serum sialic acid vs. FPG	0.737(+)	HS
Serum sialic acid vs. PPBG	0.846(+)	HS
Serum sialic acid vs. HbA1c	0.802(+)	HS
Serum sialic acid vs. serum creatinine	0.719(+)	HS
Serum sialic acid vs. blood urea	0.817(+)	HS
Serum sialic acid vs. 24-h urinary albumin	0.714(+)	HS
Serum sialic acid vs. e-GFR	0.936(-)	HS
Serum sialic acid vs. serum triglycerides	0.738(+)	HS
Serum sialic acid vs. serum cholesterol	0.942(+)	HS
Serum sialic acid vs. BMI	0.474(+)	S
Serum sialic acid vs. age of the patients at the onset of the discovery of DM	0.262(-)	NS
Serum sialic acid vs. duration of DM	0.145(-)	NS

BMI = body mass index, DM = diabetes mellitus, FPG = fasting plasma glucose, PPBG = postprandial blood glucose, HbA1c = glycated hemoglobin, e-GFR = estimated glomerular filtration rate, HS = highly significant, S = significant, NS = non-significant

no significant correlation between sialic acid and the age of the patients at the onset of the discovery of DM and duration of DM in the diabetic nephropathic group [Table 4].

Linear regression analysis for the prediction of serum creatinine level showed that the parameters of glycemic control (FPG, PPBG, and HbA1c), 24-h urinary albumin, and sialic acid level were considered as a significant predictor of serum creatinine level [Table 5].

Linear regression analysis for the prediction of urinary albuminuria showed that FPG, PPBG, HbA1c, sialic acid, and duration of DM were considered as a significant predictor of albuminuria [Table 6].

Linear regression analysis for predictors of serum sialic acid showed that parameters of glycemic control (FPG, PPBG, and HbA1c) were considered as a significant predictor of the serum sialic acid level [Table 7].

Table 5: Linear regression analysis for prediction of serum creatinine level

Model	Standardized coefficients	*t*	*P* value
	Beta		
Age	0.028	0.742	0.470
BMI (kg/m^2)	0.044	1.433	0.174
FPG (mg/dL)	0.547	2.177	0.047*
PPBG (mg/dL)	0.022	2.214	0.034*
HbA1c	0.630	2.421	0.023*
24-h albumin	1.161	5.226	0.000*
Sialic acid (ug/mL)	0.301	-2.387	0.032*
Blood urea (mg/dL)	-0.028	-0.131	0.898
e-GFR	0.086	-0.803	0.435
Duration of DM	0.022	0.829	0.421
R	**Adjusted R^2**	***F* test**	***P* value**
0.997	0.989	218.9	0.001

BMI = body mass index, DM = diabetes mellitus, FPG = fasting plasma glucose, PPBG = postprandial blood glucose, HbA1c = glycated hemoglobin, e-GFR = estimated glomerular filtration rate
*significant

Table 6: Linear regression analysis for prediction of urinary albuminuria

Model	Standardized coefficients	*t*	*P* value
	Beta		
Age	-0.007	-0.256	0.802
BMI (kg/m^2)	0.007	0.295	0.772
FPG (mg/dL)	0.286	2.514	0.022*
PPBG (mg/dL)	0.192	2.302	0.054*
HbA1c	0.570	5.226	0.000*
Sialic acid (ug/mL)	-0.281	-2.879	0.019*
e-GFR	0.072	0.974	0.346
Duration of DM	0.299	2.359	0.033*
Serum creatinine (mg/dL)	0.052	1.338	0.202
Blood urea (mg/dL)	-0.005	-2.267	0.794
R	**Adjusted R^2**	***F* test**	***P* value**
0.998	0.995	447.46	0.000

BMI = body mass index, DM = diabetes mellitus, FPG = fasting plasma glucose, PPBG = postprandial blood glucose, HbA1c = glycated hemoglobin, e-GFR = estimated glomerular filtration rate
*significant

Discussion

Serum sialic acid is considered as one of the acute phase reactant response.[10] The negative charge of the glomerular basement membrane is maintained by the sialic acid, and this is important for the membrane permeability. Increased vascular permeability with subsequent release of endothelial sialic acid in the circulation leads to increased serum sialic acid level.[7] Diabetic nephropathy (DN) is leading cause of end-stage renal disease worldwide.[11] Our study showed that on comparing between diabetic patients and control group patients we found that sialic acid is increased in the diabetic group more than the control group and this was statistically significant [Table 4], sialic acid level and (fasting blood glucose, postprandial blood glucose, HBA1C) were found to be positively correlated [Table 7] and these parameters were considered as predictors of serum sialic acid level [Table 10].

This was concordant with Divija *et al*.[12] who revealed that serum sialic acid was positively correlated with HBA1c, fasting blood glucose, and postprandial blood glucose in the diabetic cases indicating a linear increase relationship between these parameters. Subzwari and Qureshi[13] revealed a significant increase of serum sialic acid among

Table 7: Linear regression analysis for predictors of serum sialic acid

Model	Standardized coefficients	*t*	*P* value
	Beta		
BMI (kg/m^2)	0.126	-1.582	0.136
FPG (mg/dL)	0.796	9.106	0.001*
PPBG (mg/dL)	0.397	3.009	0.004*
HbA1c	0.365	2.762	0.008*
Serum creatinine (mg/dL)	0.150	-0.214	0.834
Blood urea (mg/dL)	0.924	1.839	0.087
Urinary albuminuria	0.856	-0.879	0.394
e-GFR	0.129	0.169	0.868
R	**Adjusted R^2**	***F* test**	***P* value**
0.978	0.925	30.67	0.000

BMI = body mass index, FPG = fasting plasma glucose, PPBG = postprandial blood glucose, HbA1c = glycated hemoglobin, e-GFR = estimated glomerular filtration rate

*significant

the subjects with diabetes compared to the control subjects. Serum and urine sialic acid concentration increased in patients with diabetes as compared to the general population, especially in patients with type 2 diabetes. Ghosh *et al.*[14] revealed that serum sialic acid levels were found to be significantly increased in diabetes without nephropathy compared to controls. Poddar and Ray[15] revealed that a clear-cut elevation in sialic acid levels is evident from the data in diabetics without complications as compared to the healthy controls.

In our study, serum sialic acid level was positively correlated with BMI, cholesterol, and TG [Table 7]. This was in concordant with Englyst *et al.*[16] who found that fasting sialic acid level is affected by the total body fat and it is considered as a predictor for it. We found that if the body fat is equal the serum sialic acid concentration was higher when comparing diabetic patients with the control group. And this was concordant with Browning *et al.*[17] who found a significant association between SA and metabolic syndrome, also this was in agreement with Subzwari and Qureshi[13] who found factors such as cholesterol, LDL, and TG were associated with increased serum sialic acid concentration.

A positive significant correlation was found between sialic acid level and DN parameters (creatinine, urea, 24-h urinary albumin, and e-GFR) [Table 7], and sialic acid level was considered as a significant predictor of serum creatinine and urinary albuminuria (nephropathic parameters) [Tables 5 and 6].

This result was in agreement with a study by Ghosh *et al.*[14] who revealed that serum sialic acid levels were found to be significantly increased in diabetes with or without nephropathy compared to controls and also revealed a very large positive correlation between serum sialic acid and urinary microalbumin, which showed that as microalbumin excretion increases, serum sialic acid also increases pointing to a contributory role of serum sialic acid toward renal damage. These findings indicate that serum sialic acid increases with the severity of diabetic renal complications.

Kumar *et al.*[18] revealed a significant positive correlation between serum sialic acid and creatinine excretion, serum sialic acid, and serum creatinine levels; and a statistically significant difference was observed in the values of serum creatinine, serum sialic acid, and controls. It was also observed that serum sialic acid concentrations were strongly associated with several risk factors such as renal dysfunction (creatinine) and urine albumin excretion for the development of micro- and macrovascular complications. These markers were clinically correlated with the increasing concentration of sialic acid. Divija *et al.*[12] revealed a significant positive correlation between serum sialic acid with blood urea, serum creatinine, systolic, and diastolic blood pressure in cases, indicating that as sialic acid increases, these parameters also increases. Subzwari and Qureshi[13] revealed a significant increase of serum sialic acid among the subjects with diabetes compared to the control subjects. Furthermore, in the subjects with diabetes, urine sialic acid and microalbumin were significantly higher. The sialic acid values were statistically significantly higher with the increased urinary albumin excretion. Krishnamurthy *et al.*[19] revealed a progressive rise in serum sialic acid levels with urinary albumin excretion and a significant positive correlation between them. It is noted that there was a significant difference in serum sialic acid levels between controls and normoalbuminuric patients, which was not shown with serum creatinine and albumin excretion levels. Serum creatinine showed a significant increase only in microalbuminuric patients, suggesting its importance only after the onset of nephropathy. Therefore, sialic acid may act as an indicator of the early diabetic process. Roozbeh *et al.*[6] revealed that the serum and urine levels of SA and neuraminidase activity were always abnormally higher in diabetic nephropathic patients when compared to diabetic patients with no nephropathy or nephropathic patients, which is expected as both conditions of diabetes and nephropathy may cause an increase in these variables. Abdella *et al.*[20] revealed a progressive elevation in total sialic acid concentrations with increased urinary albumin excretion. The differences in total sialic acid levels among the normoalbuminuric, microalbuminuric, and macroalbuminuric diabetic groups were significant. Yokoyama *et al.*[21] revealed that serum sialic acid concentration was increased in patients with clinical nephropathy compared with normoalbuminuric patients, and UAE (urinary albumin excretion) was significantly correlated independently with serum sialic acid. Chen *et al.*[22] revealed that there was a progressive rise in serum sialic acid concentrations with increasing UAE in non-insulin-dependent diabetes mellitus (NIDDM) patients. Furthermore, normoalbuminuric NIDDM patients had

elevated serum sialic acid concentrations compared with healthy nondiabetic control subjects, suggesting an effect *per se* of the diabetic state. Ozben *et al.*[23] revealed that there was a significant correlation between sialic acid and albumin excretions. This may suggest that sialic acid and albumin excretions may occur at the same time, or sialic acid may follow the onset of albuminuria. However, the total sialic acid excretion rate in the normoalbuminuric group was higher than the range found in healthy subjects. Thus, increased urinary excretion of total sialic acid in normoalbuminuric patients may precede the onset of microalbuminuria. However, to prove this hypothesis, long-term follow-up studies are required. Poddar and Ray[15] found that on comparing diabetic patients without complication with a healthy control there was a marked elevation of serum sialic acid level and also is was more evident in diabetic subjects with complications as they showed a higher levels.

Tomino *et al.*[24] found that the levels of sialic acid in sera from DN patients were significantly increased, but they found no significant correlation between the levels of blood urea nitrogen, serum creatinine or proteinuria, and sialic acid. Although an increase of sialic acid in sera is observed in patients with various kinds of inflammatory diseases and cancers, this is considered to be nonspecific phenomena.

Conclusion

We found that there was a significant positive correlation between serum sialic acid and FPG, PPBG, HbA1c, BMI, serum creatinine, blood urea, urinary albuminuria, triglycerides, and cholesterol in patients with DN, and a significant negative correlation with estimated GFR, and also there was no significant correlation between sialic acid and age of patient at the onset of the discovery of DM and duration of DM in the diabetic nephropathic group so it can be considered as a sensitive marker for diabetic microvascular complications.

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Conflicts of interest

There are no conflicts of interest.

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