

Clinical correlation between frequent risk factors of diabetic nephropathy and serum sialic acid

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Abstract

Background: It has been recently established that serum sialic acid is a potent cardiovascular and renal risk factor in the general population and elevated in diabetic type 2 patients. This study was designed to assess the coexistence of frequently documented risk factors of diabetic nephropathy with serum sialic acid. **Methods:** A total of 100 diabetic patients (50 with and 50 without nephropathy) aged 47.56 ± 10.68 (mean \pm SD) years attending several diabetic clinics in the private sector in Karachi were included after informed consent was obtained. Systolic and diastolic blood pressures were recorded by standard mercury sphygmomanometer. Fasting blood samples were collected for estimations of blood glucose, HbA1c, serum urea, creatinine and sialic acid levels. **Results:** Serum sialic acid, glucose, HbA1c, urea and creatinine levels were increased significantly ($P < 0.01$) in patients with diabetic nephropathy compared to diabetic patients without nephropathy. Regression and correlation analysis showed a significant positive correlation between serum sialic acid and fasting blood glucose, HbA1c, serum urea and creatinine levels. Body Mass Index and blood pressure were also significantly higher in diabetic patients with diabetic nephropathy compared to those without nephropathy. Fifty four percent of diabetic nephropathy patients were smokers compared with 41% of patients in the control group (diabetic patients without nephropathy). **Conclusion:** It is concluded that elevated serum sialic acid level is strongly associated with the presence of nephropathy, a microvascular complications of diabetes. As there is a significant unvaried link between serum sialic acid and diabetic nephropathy, consideration of sialic acid as potent disease marker for diabetic nephropathy is justified. (Int J Diabetes Metab 14: 138-142, 2006)

Introduction

Serum or plasma sialic acid (N-acetyl neuraminic acid), an inflammatory marker, has recently been shown to be a strong predictor of cardiovascular mortality.^{1,2} Several general population studies and those carried out in diabetic patients with complications have pointed to serum sialic acid as a marker of inflammation in cardiovascular disease.^{3,4} Sialic acid is released from the terminal oligosaccharide chains of some glycoproteins and glycolipids in the acute phase of inflammation.⁵

Diabetes mellitus is a chronic metabolic disorder that can lead to severe cardiovascular, renal, neurologic and retinal complications.^{6,7} Diabetic nephropathy affects more than 30% of type 1 diabetic patients and it is a leading cause of end stage renal disease.⁸ A number of risk factors have been associated with the metabolic syndrome, including hypertension, poor glycemic control, central obesity, smoking, dyslipidemia and glycated end products.⁹ Serum sialic acid is a newly established potential risk factor for the development of macro- and microvascular complications of diabetes. The current study was designed to investigate the significance of serum sialic acid as a major risk factor in the

development of diabetic nephropathy and to observe the clinical relationship of serum sialic acid with other markers of diabetic nephropathy.

Subjects and Methods

A total of 100 previously diagnosed type 2 diabetic patients, (50 with and 50 without nephropathy) attending several diabetic clinics in the private sector in Karachi were included in the present study after informed consent was obtained. The selection criteria was based on WHO criteria.¹⁰ Their mean age was 47.56 ± 10.68 years. Patients suffering from type 1 diabetes mellitus, gestational diabetes and any known mental illness, macrovascular disease prior to diagnosis of type 2 diabetes, or the patients who refused to participate in the study were excluded. Fifty healthy subjects with no known history of hyperglycemia and renal disease were included as control.

A previously structured questionnaire was used to record the demographic features of all subjects. Height and weight were noted for BMI (Body Mass Index=weight in kg/height in m²). BMI from 20.0 to 29.9 was considered overweight and >30.0 was considered as obese. Blood pressure was measured with a standard mercury sphygmomanometer while the patient was sitting after resting for 10 min. Hypertension was defined as blood pressure $\geq 140/90$ mm Hg.¹¹ Patients were classified as smokers if they smoked more than one cigarette a day.

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Table 1: Biochemical parameters in diabetic patients with and without nephropathy as compared to control.

Parameters	Control	Diabetic patients	Diabetic nephropathy patients
Serum sialic acid (mmol/L)	1.72 ± 0.36	1.95 ± 1.25*	2.21 ± 0.37*
Blood glucose (mmol/L)	5.4 ± 0.5	9.0 ± 3.9*	11.9 ± 3.4*
HbA1c (%)	4.6 ± 1.6	7.3 ± 2.0*	9.3 ± 1.9*
Serum urea (mmol/L)	10.6 ± 2.6	10.7 ± 1.9	19.4 ± 4.9*
Serum creatinine (µmol/L)	107.7 ± 48.8	112.8 ± 38.4	198.3 ± 29.9*

Values are Mean ± SD

P<0.01 as compared to control subjects

Table 2: Physical parameters in diabetic patients with and without nephropathy as compared to control.

Parameters	Control	Diabetic patients	Diabetic nephropathy patients
Systolic BP (mm Hg)	123.8 ± 8.2	125.3 ± 6.3	149.0 ± 16.7*
Diastolic BP (mm Hg)	79.4 ± 6.8	78.7 ± 4.1	92.6 ± 8.0*
BMI (Kg/m ²)	21.4 ± 2.6	27.2 ± 2.6*	36.7 ± 2.2*
Smoking (%)	00	41	54

Values are Mean ± SD

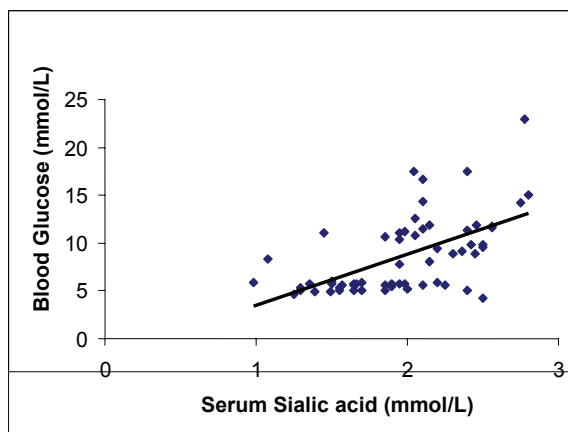
P<0.01 as compared to control subjects

Table 3: Correlation between serum sialic acid and frequent risk factors in diabetic patients without nephropathy.

	r =	P Value
Blood glucose	0.22	Non significant
HbA1c	0.28	Non significant
Serum urea	0.09	Non significant
Serum creatinine	0.15	Non significant
SBP	0.03	Non significant
DBP	0.20	Non significant
BMI	0.25	Non significant

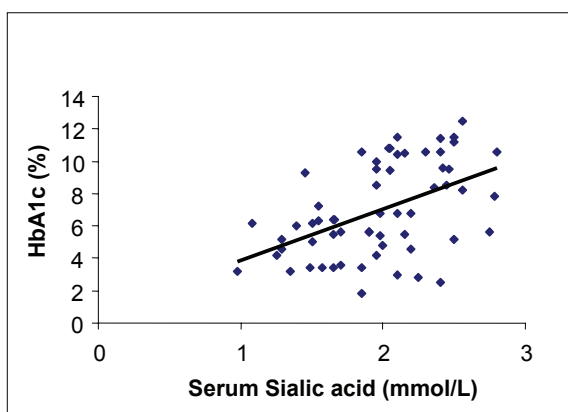
Fasting blood samples were collected in lithium-heparin coated tubes after no medications were taken for the previous 12 h or longer. Serum sialic acid was estimated by Ehrlich's method.¹² HbA1c was estimated by Fast Ion-Exchange Resin Separation Method (Human Gessellschaft fur Biochemica und Diagnostica mbH, Germany). Fasting blood glucose was measured by the o-toluidine method.¹³ Serum urea was estimated by the thiosemicarbazide-diacetyl monoxime method.¹⁴ Serum creatinine was measured by the modified Jaffe's method.¹⁵

Results are presented as mean ± SD. Statistical signifi-



r = 0.58 (p<0.01)

Fig 1: Correlation between serum sialic acid and blood glucose in diabetic patients with nephropathy.



r = 0.58 (p<0.01)

Fig 2: Correlation between serum sialic acid and HbA1c in diabetic patients with nephropathy.

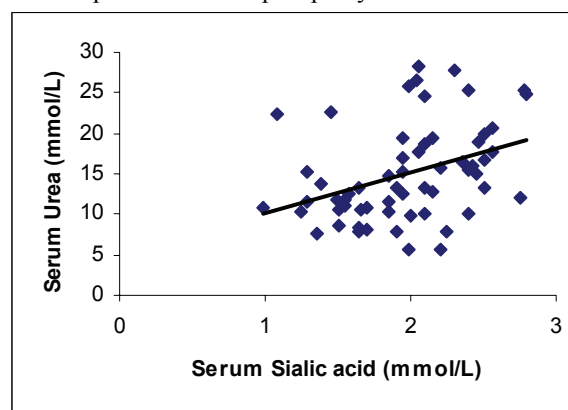
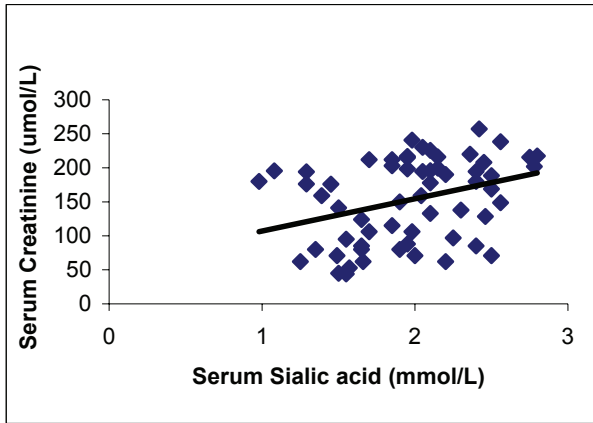


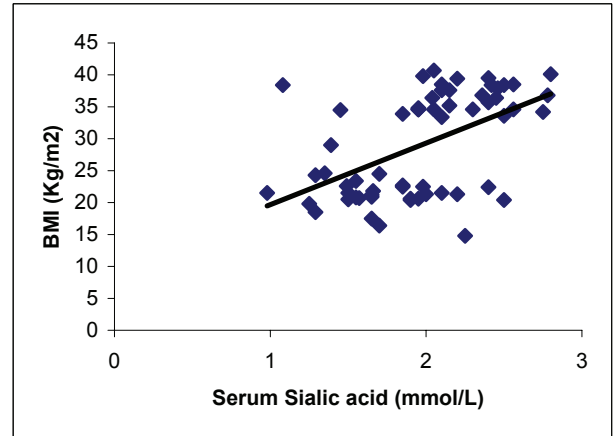
Fig 3: Correlation between serum sialic acid and serum urea in diabetic patients with nephropathy.

cance and difference from control and test values were evaluated by Student's t-test. Correlation coefficient and regression analysis were used to describe the effects of elevated serum sialic acid levels on glucose, HbA1c, urea, creatinine, SBP, DBP and BMI. A scattergram was plotted by taking dependent variables on the y-axis and the independent variable (sialic acid) on the x-axis.



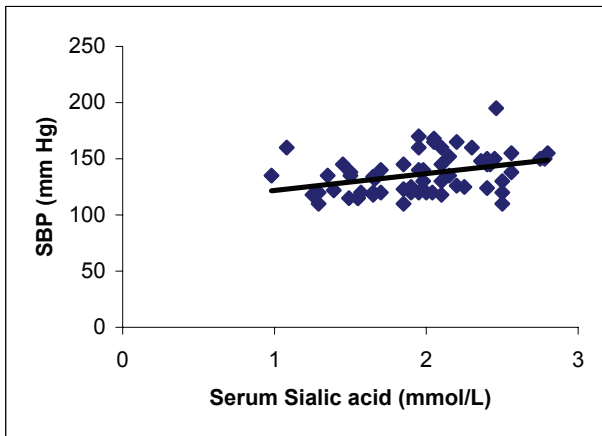
$r = 0.34$ ($p < 0.05$)

Fig 4: Correlation between serum sialic acid and serum creatinine in diabetic patients with nephropathy.



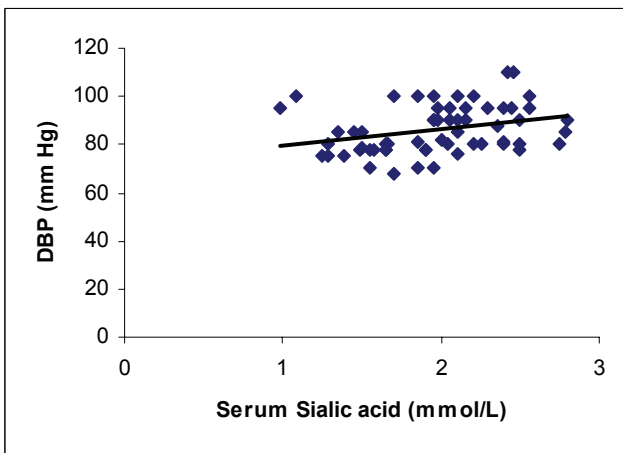
$r = 0.52$ ($p < 0.01$)

Fig 7: Correlation between serum sialic acid and BMI in diabetic patients with nephropathy



$r = 0.36$ ($p < 0.05$)

Fig 5: Correlation between serum sialic acid and SBP in diabetic patients with nephropathy



$r = 0.31$ ($p < 0.05$)

Fig 6: Correlation between serum sialic acid and DBP in diabetic patients with nephropathy.

Results

Serum sialic acid, blood glucose and HbA1c were increased significantly ($P < 0.01$) in both diabetic and diabetic nephropathy patients as compared to control subjects. This

elevation was higher in diabetic nephropathy patients compared to those without nephropathy (Table 1).

Serum urea and creatinine levels were increased significantly ($P < 0.01$) in patients with diabetic nephropathy compared to control subjects. No significant elevation in serum urea and creatinine levels was observed in diabetic patients without nephropathy compared to control (Table 1).

Systolic and diastolic blood pressures were raised significantly ($P < 0.01$) in patients with diabetic nephropathy whereas no significant change was observed in diabetic patients as compared to control subjects (Table 2). BMI was significantly ($P < 0.01$) increased in both diabetic nephropathy patients and diabetic patients without nephropathy as compared to control subjects (Table 2).

Regression and correlation analysis showed a significant positive correlation between serum sialic acid and blood glucose ($r = 0.58$, $P < 0.01$), HbA1c ($r = 0.48$, $P < 0.01$), serum urea ($r = 0.37$, $P < 0.05$) and serum creatinine ($r = 0.34$, $P < 0.05$) in diabetic nephropathy patients (Figs 1-4). Systolic ($r = 0.36$, $P < 0.05$) and diastolic ($r = 0.31$, $P < 0.05$) blood pressures were also positively correlated with serum sialic acid in diabetic nephropathy patients (Figs 5 and 6). A significant positive correlation was also observed between serum sialic acid and BMI ($r = 0.52$, $P < 0.01$) (Fig 7).

No significant correlation between serum sialic acid and blood glucose, HbA1c, serum urea, serum creatinine, systolic and diastolic blood pressure and BMI was observed in diabetic patients without nephropathy (Table 3).

Discussion

The present study demonstrates the increase in serum sialic acid in diabetic patients with the progression of complications such as nephropathy. We also observed that serum sialic acid concentrations were significantly associated with several known risk factors, notably glycemic control (HbA1c), renal dysfunction (urea and

creatinine), hypertension and smoking for the development of diabetic micro and macrovascular complications. The results are completely in accordance with recent studies in the same area.^{16,17} A relationship between serum sialic acid and microvascular complication has been observed before in small scale studies for type 1 and type 2 diabetes.^{18, 19}

Serum sialic acid is a marker of the acute phase response.^{2,20} Acute phase glycoproteins with sialic acid as a component of the oligosaccharide side chains are produced by the liver and stimulated by proinflammatory cytokines. Tissue injury caused by diabetic vascular complications stimulates local cytokine secretion from cells involved in the complications, such as endothelium and macrophages that are known to be the major sources of cytokine production²¹, and this induces an acute phase response. The diabetic process stimulates cytokine production from cells throughout the body, and these cytokines play a direct role in the development of vascular complication. This hypothesis is supported by evidence that proinflammatory cytokines cause endothelial dysfunction by increasing capillary permeability, inducing prothrombotic properties and promoting leukocyte recruitment by synthesis of adhesion molecules and chemoattractants.²²

Cytokinaemia from a variety of sources may lead to microvascular abnormalities. The need for early predictors of diabetic vascular complications, such as nephropathy, has recently been reviewed.²³ Some patients with microalbuminuria have advanced renal structure changes and microalbuminuria may be a marker of microvascular damage that has already occurred.²⁴ If circulating sialic acid increases before microangiopathy develops, it may be an early signal of processes such as hypercytokinaemia that cause, or drastically increase, the risk of renal failure.

In conclusion, the present study suggests that increased serum sialic acid levels are strongly associated with the development of diabetic nephropathy. The markers of glycaemic control (blood sugar and HbA1c) and renal insufficiency (serum urea and creatinine), hypertension and obesity are clinically correlated with increasing concentration of sialic acid. These findings strengthen the hypothesis that an increase in circulating serum sialic acid is an early manifestation of diabetic renal disease. Further research would be of help to clarify the role of sialic acid in the development of diabetic renal disease.

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