Association of Serum Sialic Acid With Cardiovascular Metabolic Risk Factors in Kuwaiti Children and Adolescents With Type 1 Diabetes

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The aim of the present study was to investigate the relation of serum total sialic acid (TSA) concentrations with cardiovascular metabolic risk factors in Kuwaiti children and adolescents with uncomplicated type 1 diabetes. This case-control study included 150 (57 males and 93 females) type 1 diabetic children aged 6 to 18 years matched by age and sex to 150 nondiabetic children as controls. Measured variables included weight, height, systolic, diastolic blood pressure, and biochemical variables: blood glucose, glycated hemoglobin (HbA_{1C}), triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL), apolipoproteins (apo) A1 and B, and urine microalbumin. There was no significant difference between mean serum TSA of the type 1 diabetic children (671.0 mg/L) and their controls (663.7 mg/L). In diabetic children, mean serum TSA was significantly higher in females (699.1 mg/L) than in males (625.2 mg/L) ($P = .003$). Significant correlations were found between serum TSA and the cardiovascular risk factors TC ($P = .002$), TG ($P < .001$), and apo B ($P = .008$). TSA mean level was significantly higher in diabetic children with poor glycemic control ($HbA_{1C} > 9.0\%$; $P = .015$), raised TC ($P = .013$), raised TG ($P = .014$), and in children with family history of cardiovascular disease (CVD; $P = .02$). In conclusion, the study suggests that serum TSA levels were not elevated in young type 1 diabetic children as compared with controls. The study also confirmed significant correlation of TSA concentrations with CVD risk factors TC, TG, and apo B, and as such serum TSA may be considered as a marker for CVD risk, especially in diabetic patients. A long-term prospective study is recommended to ascertain the longitudinal relationship of serum TSA with the adverse metabolic changes in type 1 diabetic children as complications prevail.

SIALIC ACID is a terminal component of the nonreducing end of carbohydrate chains of glycoproteins and glycolipids, which are essential constituents of many hormones and enzymes present in serum and tissues. Serum sialic acid is almost completely bound to glycoproteins and lipids. The degree of sialylation is believed to be responsible for the negative charge of glycoproteins and for the pathogenesis of atherosclerosis. Serum total sialic acid (TSA) has received considerable attention as a possible marker for cardiovascular (CVD) disease and mortality.[1] Some investigators have reported that serum TSA concentrations were not elevated in subjects with type 1 diabetes without tissue complications, in comparison to nondiabetic subjects.[2] Others have reported that circulating serum TSA concentrations were higher in patients with microvascular complications.[3-5]

Studies on serum TSA in subjects with type 1 diabetes have been conducted on Caucasians. There have been no studies of this type, to our knowledge, on subjects from the Arab countries. Also, most of these studies on Caucasians were conducted on older type 1 diabetic patients rather than on children. Arab populations may vary from Caucasian populations regarding type 1 diabetes and the factors associated with the disease, since type 1 diabetes is the outcome of environmental, genetic, and immunologic interactions. Hence, racial or ethnic background represents an important risk factor for type 1 diabetes as it reflects environmental and genetic differences. This justifies the importance of studying type 1 diabetes in various populations.

In Kuwait, there has been an almost 4-fold increase in the incidence of type 1 diabetes during the last 2 decades.[6] This increase probably indicates the role played by environmental factors in a genetically susceptible population.[7] Also, genotype distributions in diabetic and nondiabetic Kuwaiti children differ from other populations.[8] CVD is the first underlying cause of death in Kuwait, and death from CVD is about 2 to 4 times higher in diabetic patients as compared with nondiabetic subjects.[9] Therefore, there is strong reason for examining circulating TSA concentrations as a marker of predisposition to CVD in children with type 1 diabetes. The aim of the present study was to investigate the relation of serum TSA concentrations with cardiovascular metabolic risk factors in young Kuwaiti children and adolescents with uncomplicated type 1 diabetes.

MATERIALS AND METHODS

Patients

This case-control study included 150 Kuwaiti Arab diabetic children with type 1 diabetes matched by age and sex to 150 nondiabetic healthy Kuwaiti Arab children as controls (57 males and 93 females). Their mean age (SD) was 12.85 (3.08) and 12.88 (3.09) for diabetic and nondiabetic children, respectively (age range, 6 to 18 years). The 2 groups were comparable as they had similar gender, age, and socioeconomic status compositions. Controls were randomly selected from the same classes of the diabetic children. Diagnosis of type 1 diabetes mellitus was based on the World Health Organzation (WHO)[10] and the American Diabetes Association[11] criteria to ensure appropriate selection of cases. None of the patients was taking any medication other than

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insulin, or had any recognized complications of diabetes. Furthermore, none of the children presented any disease known to affect lipoprotein metabolism, and none of them had known malignant disease or infection at the time of the study. The Medical Research Ethics Committee of the Faculty of Medicine, Kuwait University approved the study protocol. Informed consent was obtained from parents of included children before their enrolment in the study. Blood samples were obtained after agreement of the children.

Anthropometric Measurements and Blood Pressure

Weight and height were measured with the child wearing light clothes and bare-footed. Weight was recorded to the nearest 0.1 kg using the electronic personal scale Seca 708 (Seca Corp, Columbia, MD). Height was measured to the nearest 0.5 cm by the stadiometer with the child's heels, back, and occiput touching the vertical bar. The body mass index (BMI, weight in kilograms/height in meters squared) was used as an index for obesity.

Blood pressure was measured using standard mercury sphygmomanometer, Littman classic II stethoscope (Stethoscope Technical Services, St Paul, MN), and 3 different size cuffs to allow for choice of the suitable size for the child. To relieve nervous tension, children were seated 5 minutes before checking their blood pressure, then 2 readings were recorded on the right arm of the child and the second reading was used in the analysis. The same blood pressure instrument was used throughout the study and was checked periodically for loss of mercury height or leak in the tubing or the control valves.

Biochemical Analyses

Venous blood samples were obtained before breakfast following an overnight fast (12 to 14 hours). Serum samples were immediately separated from erythrocytes and stored frozen at −20°C. All lipid determinations were processed in the accredited laboratories of the Amiri University teaching hospital. Blood glucose (FBG), triglycerides (TG), and total cholestrol (TC) were analyzed on Beckman Synchron CX5 (Beckman Instruments, Galway, Ireland) by enzymatic time endpoint methods.[12-14]

High-density lipoprotein cholesterol (HDL) was measured on the Discrete Clinical Analyzer ACA (Dupont, Wilmington, DE). This method is based on separation of lipoproteins by a polyanion reagent followed by enzymatic cholesterol analysis. Low- and very-low-density lipoprotein (LDL and VLDL) are qualitatively precipitated by a buffered phosphotungstate reagent. The HDL fraction present in the supernatent is then analyzed by the "ACA" enzymatic method.[15] The atherogenic index (AI) was calculated as AI = (TC − HDL)/HDL.

Apolipoproteins (apo) A1 and B were measured on Beckman Array by immunonephelometry. Antibody to human apo A and apo B is brought into contact with human apo A and apo B, respectively, in the sample. The increase in light scatter resulting from the antibody-antigen reaction is converted to a peak rate signal, which is a function of the concentration of analyte.[16] Coefficient of variation values of ≤5% were obtained with the apo A1 and apo B tests for within-run precision and of ≤8% for between-run precision. The ratio apo B/apo A1 was calculated.

Glycated hemoglobin (HbA_{1C}) was measured on Beckman Synchron CX7 using Tina-Quant HbA_{1C} Kits (Boehringer Mannheim, Tutzing, Germany). The assay is based on the immunoturbidemetric determination of HbA_{1C}.[17] HbA_{1C} reacts with anti-HbA_{1C} to give a soluble immunocomplex. Polyhaptens then bind to excess antibodies and the resulting agglutinated complexes are measured turbidemetrically. Total hemoglobin is measured simultaneously by photometry at 540 nm and the amount of HbA_{1C} relative to the amount of total hemoglobin is calculated. The intra-assay and interassay coefficients of variation were 3.4% and 4.5%, respectively.

Early morning urine microalbumin was determined on Beckman Array by rate nephelometry.[18] Antibody to human albumin is brought into contact with human albumin in a sample. The increase in light scatter resulting from the antibody-antigen reaction is converted to peak rate signal, which is a function of the sample albumin concentration. The coefficients of variation obtained for within-run and between-run were less than 5% and less than 8%, respectively.

Serum TSA was measured by an enzymatic colorimetric assay (reagents from Roche, Basel, Switzerland).[19,20] Glycoprotein and glycolipid bound sialic acid is hydrolyzed by neuraminidase to release free sialic acid, which is then cleaved by N-acetylneuraminic acid adolase into pyruvate and N-acetyl-D-mannosamine. Oxidation of pyruvate, catalyzed by pyruvate oxidase, yields acetyl phosphate, carbon dioxide, and hydrogen peroxide. The amount of hydrogen peroxide formed, which is equivalent to the free sialic acid, is converted by peroxidase to a red dye, which is determined colorimetrically at 550 nm.

The cut-off HbA_{1C} level for poor glycemic control was defined as greater than 9% (International Society for Pediatric and Adolescent Diabetes, ISPAD Guidelines, 2000). Similarly, TC was defined as: TC ≤ 4.3 mmol/L as the lower cut-off value, 4.4 to 5.2 as boderline, and greater than 5.2 as raised.[21] Since there is no definition for hypertriglyceridemia in children with type 1 diabetes, we adopted the European type 2 diabetes definition as: TG ≤ 1.7 mmol/L as good control, and greater than 1.7 as raised.[22] Urine micoralbumin was defined as: less than 20 mg/L as normal, and 20 to 200 mg/L as microalbumin in urine.[23]

Statistical Analysis

Data were analyzed using the Statistical Package for Social Sciences v11.0 (SPSS Inc, Chicago, IL) with a 2-sided *P* value of .05 or less as the cut-off level for statistical significance. Natural logarithms of BMI, FBG, HDL, AI, TG, apo B, and urine microalbumin were used in the analysis to normalize their distributions. The nonparametric Wilcoxon singed rank test was used to compare 2 non-normal variables, while the paired *t* test was used to compare means of 2 normally distributed variables. Student's *t* test was used to compare between 2 independent means, while analysis of variance (ANOVA) was used to compare between more than 2 independent means. Correlations were used to assess the association between TSA concentrations and other variables.

RESULTS

In the diabetic group, the median diabetes duration was 4 years, and the median age of diabetes onset was 9 years: 9.50 years in males and 8 years in females. The median number of insulin injections per day was 2 (range, 1 to 4). The method of administering insulin was mostly (96.6%) by needle injection.

Table 1 summarizes the clinical and biochemical profiles of type 1 diabetic children and controls. There was no significant difference between mean serum TSA in children with type 1 diabetes (671.0 mg/L) and their controls (663.7 mg/L). The mean serum TSA in female diabetic children (699.1 mg/L) was slightly higher than in the female controls (657.2 mg/L), but the difference was not significant. However, in the diabetic group the mean serum TSA level was significantly higher in females (699.1 mg/L) than in males (625.2 mg/L) ($P = .003$).

The mean TC, apo A1, apo B, and HDL concentrations were significantly higher in diabetic children than in nondiabetic controls, ($P < .001$ in TC, apo A1, and apo B; $P < .01$ in HDL). In female diabetic children, the mean TC concentration was significantly higher (4.74 mmol/L) than in female controls (4.24 mmol/L), $P < .001$. In addition, the mean apo A1 concentration (1.42 g/L) and the mean apo B concentration (0.85 g/L) were significantly higher in female diabetic children

Table 1. Clinical and Biochemical Profiles of Type 1 Diabetic and Nondiabetic Kuwaiti Children Aged 6 to 18 Years

	Males		Females		All	
	Nondiabetic Controls	Type 1 Diabetic Children	Nondiabetic Controls	Type 1 Diabetic Children	Nondiabetic Controls	Type 1 Diabetic Children
n	57	57	93	93	150	150
Age (yr)	13.37 ± 2.85	13.47 ± 2.95	12.57 ± 3.20	12.48 ± 3.10	12.88 ± 3.09	12.85 ± 3.08
TSA (mg/L)	674.3 ± 123.2	625.2 ± 155.0	657.2 ± 170.7	699.1 ± 189.0	663.7 ± 154.2	671.0 ± 180.0
BMI (kg/m^2)	23.06 ± 7.22	21.11 ± 4.52	21.03 ± 5.80	21.41 ± 6.01	21.80 ± 6.43	21.29 ± 5.48
SBP (mm Hg)	111.0 ± 11.5	111.4 ± 10.0	106.5 ± 12.9	106.8 ± 13.0	108.2 ± 12.6	108.5 ± 12.1
DBP (mm Hg)	74.5 ± 6.9	74.3 ± 7.1	71.3 ± 7.7	71.7 ± 7.7	72.5 ± 7.5	72.7 ± 7.6
FBG (mmol/L)	5.19 ± 0.42	14.20 ± 5.91†	5.21 ± 0.94	13.69 ± 5.72†	5.20 ± 0.78	13.88 ± 5.78†
HbA_{1C} (%)	5.55 ± 0.40	8.96 ± 1.74†	5.53 ± 0.63	9.35 ± 2.10†	5.54 ± 0.56	9.21 ± 1.98†
TC (mmol/L)	4.13 ± 0.66	4.38 ± 0.83	4.24 ± 0.64	4.74 ± 0.97†	4.20 ± 0.65	4.61 ± 0.93†
HDL (mmol/L)	1.07 ± 0.34	1.22 ± 0.36*	1.25 ± 0.33	1.35 ± 0.39	1.18 ± 0.35	1.30 ± 0.38*
AI	3.13 ± 1.16	2.85 ± 1.15*	2.56 ± 0.91	2.79 ± 1.35	2.78 ± 1.04	2.81 ± 1.27
TG (mmol/L)	0.83 ± 0.64	0.68 ± 0.43	0.70 ± 0.47	1.08 ± 2.52	0.75 ± 0.55	0.93 ± 2.00
Apo AI (g/L)	1.22 ± 0.17	1.34 ± 0.26	1.29 ± 0.21	1.42 ± 0.26†	1.27 ± 0.20	1.39 ± 0.26†
apo B (g/L)	0.72 ± 0.16	0.76 ± 0.20	0.71 ± 0.16	0.85 ± 0.31†	0.71 ± 0.16	0.82 ± 0.28†
apo B/apo AI ratio	0.60 ± 0.15	0.58 ± 0.15	0.56 ± 0.14	0.61 ± 0.22	0.57 ± 0.14	0.60 ± 0.20
Urine microalbumin (mg/l), median	7	5	9	10	8.0	9

NOTE. Data are expressed as mean ± SD; urine microalbumin is shown as median. Analysis used natural logarithms of BMI, FBG, HDL, AI, TG, and apo B.

*$P < 0.01$, †$P < .001$: nondiabetic *v* type 1 diabetic by paired *t* test and Wilcoxon singed rank test in urine microalbumin. In diabetic group, the mean TSA level was significantly higher in females than males, $P = .003$.

Abbreviations: TSA, serum total sialic acid; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; HbA_{1C}, glycated hemoglobin; TC, total cholesterol; HDL, high-density lipoprotein cholesterol; AI, atherogenic index; TG, triglycerides; apo A1, apolipoprotein A1; apo B, apolipoprotein B.

than in female controls (1.29 g/L and 0.71 g/L, respectively; $P < .001$). There was no significant difference in mean age, systolic (SBP) or diastolic blood pressure (DBP), or BMI between children with type 1 diabetes and controls in males and females (Table 1).

Overall, there were significant correlations between serum TSA and BMI ($r = 0.246$, $P < .001$), SBP ($r = 0.146$, $P = .012$), HbA_{1C} ($r = 0.145$, $P = .015$), TC ($r = 0.193$, $P = .001$), AI ($r = 0.156$, $P = .007$), TG ($r = 0.303$, $P < .001$), apo B ($r = 0.182$, $P = .002$), and apo B/apo A1 ratio ($r = 0.236$, $P < .001$). In diabetic children, there were significant correlations between TSA and BMI ($r = 0.214$, $P = .009$), HbA_{1C} ($r = 0.315$, $P < .001$), TC ($r = 0.251$, $P = .002$), AI ($r = 0.178$, $P = .030$), TG ($r = 0.356$, $P < .001$), apo B ($r = 0.221$, $P = .008$), and apo B/apo A1 ratio ($r = 0.271$, $P < .001$) (Table 2). There was significant correlation between TSA and diabetes duration ($r = 0.223$, $P < .01$).

When we controlled for BMI using partial correlation, significant correlations disappeared in the control group, while in the diabetic children significant correlations remained between TSA and HbA_{1C} ($r = 0.280$, $P = .001$), TC ($r = 0.184$, $P = .037$), TG ($r = 0.238$, $P = .007$), and apo B ($r = 0.174$, $P = .049$).

In the diabetic group, TSA mean level was significantly higher in females than males ($P = .003$), in children with poor glycemic control ($HbA_{1C} > 9.0\%$) than in the group with $HbA_{1C} \leq 9.0\%$, ($P = .015$). Also, TSA mean level was higher in diabetic children with raised TC ($P = .013$) or TG ($P = .014$). In addition, TSA mean level was significantly higher in diabetic children with a family history of CVD ($P = .02$). Also, in diabetic children, the mean serum TSA level was elevated as age advanced or if urine microalbumin increased; however, this increase was not statistically significant (Table 3).

DISCUSSION

It has been reported that increasing serum TSA concentrations were associated with atherosclerotic disease in diabetic patients,[1] as well as with the presence of microvascular diabetes-related complications.[3] This association of TSA may reflect an acute-phase response to an inflammatory process in the atherosclerotic development[4] or it may be the result of cytokines produced by other conditions and processes. In diabetes and hence insulin resistance, such cytokines may contribute to the development of atherosclerosis and stimulate hepatic acute-phase protein production.[24]

Our data showed no significant difference in mean serum TSA concentrations between young type 1 diabetic children and age- and sex-matched controls. This is in agreement with other studies.[2,25] However, in diabetic children the mean serum TSA concentrations was significantly higher in females than in males, which confirms a sex difference in keeping with Crook et al.[2] Also, the mean serum TSA level was higher in diabetic female children than in their controls. The justification of this difference is not clear, but one speculation is that a higher acute-phase response in diabetic females may reflect the fact that females with diabetes lose the protection from CVD enjoyed by nondiabetic females. Hence, there is increased cardiovascular risk in diabetic than in nondiabetic females.[2,26] Differences in lipid and lipoproteins levels were observed

Table 2. Association Between TSA and Clinical and Biochemical Variables in Type 1 Diabetic and Nondiabetic Kuwaiti Children

	TSA (mg/L)					
	Nondiabetic Controls (n = 150)		Type 1 Diabetic Children (n = 150)		All (N = 300)	
	r	*P*	*r*	*P*	*r*	*P*
BMI (kg/m^2)	0.284	<.001	0.214	.009	0.246	<.001
SBP (mm Hg)	0.171	.036	0.123		0.146	.012
DBP (mm Hg)	0.126		0.090		0.107	
FBG (mmol/l)	0.059		0.128		0.082	
HbA_{1C} (%)	0.074		0.315	<.001	0.145	.015
TC (mmol/L)	0.099		0.251	.002	0.193	.001
HDL (mmol/L)	−0.077		−0.099		−0.085	
AI	0.127		0.178	.030	0.156	.007
TG (mmol/L)	0.225	.006	0.356	<.001	0.303	<.001
Apo AI (g/L)	−0.069		−0.014		−0.029	
Apo B (g/L)	0.120		0.221	.008	0.182	.002
apo B/apo A1 ratio	0.179	.030	0.271	.001	0.236	<.001
Urine microalbumin (mg/L)	−0.043		0.066		0.023	

NOTE. Analysis used natural logarithms of BMI, FBG, HDL, AI, TG, apo B, and urine microalbumin. *P* values for non–statistically significant correlations ($P > .05$) were left blank. Significant correlation between TSA and diabetes duration ($r = 0.223$, $P < .01$).

Abbreviations: TSA, serum total sialic acid; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; HbA_{1C}, glycated hemoglobin; TC, total cholesterol; HDL, high-density lipoprotein cholesterol; AI, atherogenic index; TG, triglycerides; apo A1, apolipoprotein A1; apo B, apolipoprotein B,

between type 1 diabetic children compared to controls, with females being more prone to alterations of the lipid levels.[27]

Our data showed significant correlation of serum TSA concentrations with BMI, HbA_{1C}, TC, AI, TG, apo B, and apo B/apo A1 ratio in diabetic children. The significant correlation between TSA concentrations and BMI may explain the cause-effect relationship between TSA and the cardiovascular risk factors such as serum levels of TC, TG, and apo B. These correlations between serum TSA and serum lipids may be due to sialylation of lipoproteins,[2] and justify reporting TSA as a potential risk factor for coronary heart disease.[28,29] Changes in BMI are closely related to plasma insulin levels.[30,31] Insulin may enhance the synthesis of hepatic VLDL and thereby contribute to high levels of TG.[32] Insulin is also correlated with apo B and apo B/apo A1 ratio, which is considered an atherogenic risk factor.[33] In diabetic patients, insulin resistance results in elevation of serum TSA. However, it has also been suggested that serum TSA is a marker of atheroma, being increased as result of inflammatory responses due to atherosclerosis.[29] An interpretation for the relation between TSA and BMI and hence serum insulin level is that insulin is an anabolic hormone and may be involved in evoking the synthesis of sialylated proteins.[34]

Serum TSA concentrations were found significantly correlated with HbA_{1C} levels in diabetic children; this does not accord with Crook et al,[2] who reported that serum TSA concentrations were not related to indices of glycemic control in type 1 diabetic children. The mean serum TSA concentration was significantly higher in type 1 diabetic children with a family history of CVD than in those without a family history of CVD. A possible interpretation is that children with a family history of CVD are more prone to have higher incidence of CVD. The increase in TSA concentrations might reflect an ongoing atherosclerotic process.[1] Also, it has been reported[35] that TSA correlates with plasma fibrinogen level, which may explain in part the association between elevated TSA and cardiovascular disease. In the diabetic group, TSA mean level was significantly higher in females, children with poor glycemic control, elevated TC, elevated TG, and in children with family history of CVD.

Concerning microvascular diabetic-related complications, our results did not reveal significant correlation of TSA concentrations with urine microalbumin levels. The reason may be that the difference in microalbumin levels was not significant between children with type 1 diabetes and their controls. Yokoyama et al[36] reported an increase in urinary microalbumin excretion rate with elevated TSA concentrations in type 1 diabetic patients at early diabetic nephropathy. Although the cause is not known, several mechanisms have been proposed. These include shedding of TSA into the circulation as a result of vascular endothelial damage[37] and sialylated glycoproteins in the platelet plasma membrane[38] causing increased adherence of platelets to vascular endothelium. These suggestions, along with the report of increased levels of TSA in vascular endo-

Table 3. TSA Levels According to Age, Glycated Hemoglobin, Total Cholesterol, Triglycerides, Urine Microalbumin and Family History of Cardiovascular Disease in the Children With Type 1 Diabetes

Variable	TSA (mg/L) (mean ± SD)	*P* Value
Gender		.003*
Males	625.2 ± 155.0	
Females	699.1 ± 189.0	
Age (yr)		.095†
6–9	676.2 ± 110.0	
10–13	639.5 ± 144.6	
14–18	707.9 ± 226.3	
HbA_{1C} (%)		.015*
≤9.0	627.9 ± 144.7	
>9.0	700.5 ± 200.3	
TC (mmol/L)		.013†
≤4.3	648.4 ± 158.8	
4.4–5.2	651.1 ± 162.8	
>5.2	756.8 ± 227.9	
TG (mmol/L)		.014*
≤1.7	653.1 ± 159.8	
>1.7	876.8 ± 264.9	
Urine microalbumin (mg/L)		.309*
<20	660.1 ± 159.0	
≥20	701.3 ± 232.0	
Family history of CVD		.020*
No	654.1 ± 173.7	
Yes	739.0 ± 191.2	

*Student's *t* test.

†Analysis of variance (ANOVA) test.

Abbreviations: HbA_{1C}, glycated hemoglobin; TC, total cholesterol; TG, triglycerides; CVD, cardiovascular disease.

thelium,[37] raise the possibility that TSA might play a role in the pathophysiology of vascular damage. Also, there was no significant correlation between TSA and arterial SBP or DBP in diabetic children. The reason is that the young diabetic children recruited in our study had no diabetic nephropathy or atherosclerotic disease; this may be more relevant in older patients.

In conclusion, this study suggests that serum TSA levels are not elevated in young type 1 diabetic Kuwaiti children as compared with controls, but tend to be higher in females. The study also confirmed significant correlation of TSA concentrations with the cardiovascular risk factors TC, TG, and apo B, and as such serum TSA may be considered as a marker for CVD risk especially in diabetic patients. A long-term prospective study is recommended to ascertain the longitudinal relationship of serum TSA with the adverse metabolic changes in children with type 1 diabetes, which are regarded as cardiovascular risk factors for the development of atherosclerosis in adulthood.

REFERENCES

1. Lindberg G, Rastam L, Gullberg B, et al: Serum sialic acid concentration predicts both coronary heart disease and stroke mortality: Multivariate analysis including 54,385 men and women during 20.5 years follow-up. Int J Epidemiol 21:253-257, 1992
2. Crook M, Cartwright K, Lumb P, et al: Serum sialic acid in young type 1 diabetic patients. Diabetes Res Clin Pract 47:119-122, 2000
3. Crook MA, Pickup JC, Lumb PJ, et al: Relationship between plasma sialic acid concentration and microvascular and macrovascular complications in type 1 diabetes. Diabetes Care 24:316-322, 2001
4. Crook M, Earle K, Morocutti A, et al: Serum sialic acid, a risk factor for cardiovascular disease is increased in insulin-dependent diabetic patients with microalbuminurea and clinical proteinuria. Diabetes Care 17:305-310, 1994
5. Yokoyama H, Jensen JS, Jensen T, et al: Serum sialic acid concentration is elevated in IDDM especially in early diabetic nephropathy. J Int Med 237:519-523, 1995
6. Shaltout AA, Moussa MAA, Qabazard M, et al: Further evidence for the rising incidence of childhood type 1 diabetes in Kuwait. Diabet Med 19:522-525, 2002
7. Haider MZ, Shaltout A, Alsaeid K, et al: Prevalence of human leukocyte antigen DQA1 and DQB1 alleles in Kuwaiti Arab children with type 1 diabetes mellitus. Clin Genet 56:450-456, 1999
8. Al-Eisa A, Haider MZ, Srivastva BS: Angiotensin converting enzyme gene insertion/deletion polymorphism in idiopathic nephrotic syndrome in Kuwaiti Arab children. Scand J Urol Nephrol 35:239-242, 2001
9. Pyorala K, Laakso M, Uusitupa M: Diabetes and atherosclerosis: An epidemiologic view. Diabetes Metab Rev 3:463-524, 1987
10. Report of a WHO Study Group on Diabetes Mellitus, Technical Report Series 727. Geneva, Switzerland, World Health Organization, 1985
11. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 21:S5-S17, 1998 (suppl 1)
12. Public Health Service: A Proposed Method for Determining FPG Using Hexokinase and FPG-6-Phosphate Dehydrogenase. Atlanta, GA, Centers for Disease Control and Prevention, 1976
13. Bucolo G, David H: Quantitative determination of serum triglycerides by the use of enzymes. Clin Chem 19:476-482, 1973
14. Allain CC, Poon LS, Chen CS, et al: Enzymatic determination of total serum cholesterol. Clin Chem 20:470-475, 1974
15. Burstein M, Scholnick HR, Mordin R: Rapid method for isolation of lipoproteins from human serum by precipitation by polyanions. J Lipid Res 11:583-595, 1970
16. Marcovina SM, Albers JJ, Dati F, et al: International Federation of Clinical Chemistry Standardization Project for Measurements of Apolipoproteins A1 and B. Clin Chem 37:676-862, 1991
17. Palfrey S, Labib M: A rapid automated method for measuring glycated hemoglobin on the Beckman CX7 analyzer. Ann Clin Biochem 31:293-295, 1994
18. Watts GF, Bennett JE, Rowe DJ, et al: Assessment of immunochemical methods for determining low concentrations of albumin in urine. Clin Chem 32:1544-1548, 1986
19. Sugahara K, Sugimoto K, Nomura O, et al: Enzymatic assay of serum sialic acid. Clin Chim Acta 108:493-498, 1980
20. Simpson H, Chusney GD, Crook MA, et al: Serum sialic acid enzymatic assay based on microtitre plates: Application for measuring capillary serum sialic acid concentrations. Br J Biomed Sci 50:164-167, 1993
21. NCEP Expert Panel on blood cholesterol levels in children and adolescents: National Cholesterol Education Program (NCEP): Highlights of the Report of the Expert Panel on Blood Cholesterol in Children and Adolescents. Pediatrics 89:495-501, 1992
22. Alberti KGMM, Gries FA: Management of non-insulin dependent diabetes mellitus in Europe: A consensus view. Diabetic Med 5:275-281, 1988
23. Jermendy G, Farkas K, Nadas J, et al: Practical aspects of measuring microalbuminuria in diabetic patients. Diabetes Nutr Metab 14:195-200, 2001
24. Campos SP, Baumann H: Insulin is a prominent modulator of the cytokine-stimulated expression of acute-phase plasma protein genes. Mol Cell Biol 12:1789-1797, 1992
25. Crook M, Simpson H, Tutt P, et al: Serum total sialic acid and acute phase proteins in type 1 and type 2 diabetes mellitus. Clin Chim Acta 219:131-138, 1993
26. Donahue RP, Orchard TJ: Diabetes mellitus and macrovascular complications: An epidemiological perspective. Diabetes Care 15: 1141-1155, 1992
27. The DCCT Research Group: Lipid and lipoprotein levels in patients with IDDM: Diabetes Control and Complications Trial Experience. Diabetes Care 15:886-894, 1992
28. Lindberg G, Rastam L, Gullberg B, et al: Serum concentrations of total sialic acid and glycoproteins in relation to coronary heart disease risk markers. Atherosclerosis 103:123-129, 1993
29. Lindberg G, Eklund G, Gullberg B, et al: Serum sialic acid concentration and cardiovascular mortality. Br Med J 302:143-146, 1991
30. Moussa MAA, Shaltout AA, Nkansa-Dwamena D, et al: Association of fasting insulin with serum lipids and blood pressure in Kuwaiti children. Metabolism 47:420-424, 1998
31. DeFronzo RA, Ferrannini E: Insulin resistance: A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia and atherosclerotic cardiovascular disease. Diabetes Care 14:173-194, 1991
32. Lewis DF, Uffleman KD, Szeto LW, et al: Effects of acute hyperinsulinaemia on VLDL triglyceride and VLDL apo B production in normal weight and obese individuals. Diabetes 42:833-842, 1993
33. Moussa MAA, Shaltout AA, Nkansa-Dwamena D, et al: Apolipoproteins A-1 and B in Kuwaiti children. Ann Nutr Metab 42:202-210, 1998
34. Crook M, Haq M, Haq S, et al: Serum sialic acid and acute phase proteins in patients with myocardial infarction. Angiology 45:709-715, 1994
35. Haq M, Haq S, Tutt P, et al: Serum total sialic acid and

lipid-associated sialic acid in normal individuals and patients with myocardial infarction, and their relationship to acute phase proteins. Ann Clin Biochem 30:383-386, 1993

36. Yokoyama H, Jensen JS, Myrup B, et al: Raised serum sialic acid concentration precedes onset of microalbuminuria in IDDM. A 10-year follow-up study. Diabetes Care 19:435-440, 1996

37. Born GV, Palinski W: Unusually high concentrations of sialic acids on the surface of vascular endothelia. Br J Exp Pathol 66:543-549, 1985

38. Manduteanu I, Calb M, Lupu C, et al: Increased adhesion of human diabetic platelets to cultured valvular endothelial cells. J Submicrosc Cytol Pathol 24:539-547, 1992