Experimental
&
Clinical Article

Evaluation of Sialic Acid Levels in the Umbilical Cord Blood of Newborns of Diabetic and Non-Diabetic Mothers and the Relation with Poor Neonatal Outcome

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ABSTRACT

OBJECTIVE: The aim of this study is to evaluate sialic acid levels in cord blood samples of infants of natal diabetic and non-diabetic pregnancies and to assess the correlation of sialic acid levels with the poor neonatal outcomes.

STUDY DESIGN: The study was conducted between January 2016 and February 2018 with 48 diabetic patients and 39 non-diabetic patients. The inclusion criteria were participants should have an oral glucose tolerance test, patients should not have rheumatic or metabolic diseases, and the follow-up visits during whole pregnancy should be in our hospital. Sialic acid levels of the participants were assessed from the newborn cord blood within the first 6-24 hours postnatally. Also mean platelet volume, mean corpuscular hemoglobin concentration, mean corpuscular hemoglobin, platelet, bilirubin values were recorded as well as the age, gravida, parity, gestational week of the participant mothers and type of delivery, gender, weight, height and the APGAR score of the newborn, and whether insulin was used or not. SPSS statistical program was used to interpret the obtained data.

RESULTS: A total of 87 patients were included in the study, 48 from the diabetic patient group and 39 from the control group. There was no difference in sialic acid levels between the two groups (p=0.155). When the diabetic group was divided into subgroups, the group with the highest sialic acid level was type I diabetes (46.25±3.6). The others, in decreasing order, were participants with Type II diabetes (33.00±4.1) and gestational diabetes (20.87±3.7) and the difference was statistically significant (p=0.001). Those who were diabetic and on insulin treatment had significantly higher sialic acid values than those who were on diabetic diet only (p=0.007). When the sialic acid is compared in participants with higher blood glucose levels with those with a lower blood glucose level sialic acid concentration was lower in those with higher blood glucose. (p=0.006). Between these two groups, no difference was found regarding the poor neonatal outcomes and laboratory parameters (p >0.05).

CONCLUSION: Infants of diabetic and non-diabetic patients in pregnancy had no difference in sialic acid blood levels and neonatal outcomes in cord blood. However, among diabetic groups, sialic acid levels were higher in type I diabetic group than in other diabetic groups

Keywords: Diabetes mellitus, Newborn, Pregnancy, Sialic acid

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Introduction

Sialic acid (SA), is a neurominic acid derivative found in the final segments of glycoproteins, glycolipids, and oligosaccharides in human body (1). During inflammatory reactions total SA levels increase in response to increased fibrinogen and other acute-phase reactant protein levels (2,3). Sialic acid plays roles in many important cellular functions and takes part in cell structures by combining with biologically active

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molecules (4). Hydrophilic nature of SA and by forming a negative charge, SA defines the biophysical features of many biological systems. It acts as a cofactor of many cell surface receptors like insulin receptor. Inflammation plays a crucial role in the pathogenesis and complications of Type I and II diabetes, therefore, these inflammatory markers have been accepted as important indicators and determinants of the diabetic process (1). SA containing sugar chains play an imperial role in the structural and functional setting of cell biology. Serum SA levels are significantly higher in conditions such as diabetes, coronary heart disease, stroke, chronic kidney disorders, alcohol intake, and metastatic cancer. Furthermore, it is shown that an elevated level of serum SA may be taken as an important indicator of glycemic control (4).

Gestational diabetes mellitus (GDM) is one of the most common metabolic disorder of pregnancy. Macrosomia, neonatal hypoglycemia, neonatal hypocalcemia, neonatal hypomagnesemia and respiratory problems of newborn potentially occur more frequently in infants of women with GDM. Thus, glucose screening is recommended at 24^{th}-28^{th} gestational weeks to improve glycemic control. It is postulated that changes in protein composition and elevation of fibrinogen levels in diabetic patients may increase total SA levels.

The objective of this study is to evaluate the correlation between umbilical cord blood SA levels and poor obstetric outcome of diabetic and non-diabetic mothers.

Material and Method

The study is conducted at Kecioren Education and Research Hospital - Clinic of Obstetrics and Gynecology with 48 diabetic (Group A) and 39 non-diabetic (Group B) patients between January 2016 and February 2018. The study was approved by the Ethics Committee University of Health Sciences Ankara Kecioren Training and Research Hospital in Turkey (approval number: 08.08.2012 #99). The informed consent form was obtained all patient and the study was conducted in accordance with the Helsinki Declaration of 1975 on human experimentation. Diabetic patients (Group A) were divided into subgroups as Gestational diabetes, Type I diabetes and Type II diabetes. The patients who were diagnosed with gestational diabetes mellitus by oral glucose tolerance test (OGTT) were included in the study. Patients with Type I or Type II diabetes before pregnancy were also included in the study. Those patients without OGTT, those with other systemic diseases and those with rheumatic disease history were excluded from the study. Sialic acid levels were measured from the umbilical cord of newborn babies within 6-24 hours after birth. First, the samples were stored at -20°C until the time of processing. Serums were tested using the Sunredbio (Shanghai) kit on the ELİSA device consisting of EL9 Microplate reader and Model 402 Microplate washer. Prior to the study, samples and reagents were expected to reach to the room temperature, and 5 samples were prepared in different concentrations. After the microplate samples containing 96 wells and standards were pipetted, the study was carried out according to the kit procedure and the absorbance of the samples and the samples at 450 nm were studied. Calibration curve was drawn with standards and serum sialic acid levels were calculated and results were given as nmol/L. Age, gravida, parity, gestational age, insulin usage, type of delivery of the patients and infant's gender, height, weight, APGAR score, infant's stay history in the neonatal care unit and MPV, MCHC, MCH, PLT, bilirubin values in neonatal blood were also compared.

The data were analyzed with SPSS 20.0 (Statistical Package for Social Sciences Inc., IL, USA). Independent samples t-test and Pearson correlation analysis were used for the variables suitable for normal distribution, while Mann-Whitney U test and Spearman rank correlation analysis were applied for the unsuitable variables. Student's t-test was used for statistical analysis of control group and patient group parameters. The relationship between the parameters was determined by Pearson correlation analysis. Numerical values were given as mean ± standard deviation in the text and in the tables. $p<0.05$ was considered significant.

Results

A total of 87 patients (48 in the diabetic group and 39 in the control group) were included in the study. Mean Group A and Group B total serum SA levels were 46.94±3.1 and 39.99 ±3.8, respectively (Table I). There was no statistically significant difference between the two groups in terms of SA levels ($p>0.05$). When Group A was divided into subgroups according to the type of diabetes, the group with the highest SA level was the group with Type I diabetes (46.25±3.6). The other subgroups were Type II diabetes (33.00±4.1) and Gestational diabetes (20.87±3.7) in descending order. There was a statistically significant difference between these three subgroups in terms of SA level ($p=0.001$) (Table II). The levels of SA were significantly higher in insulin-regulated diabetic patients compared to diabetic patients on only dietary regulation ($p=0.007$) (Table III). SA levels were found to be higher in patients with high blood sugar when blood sugar level and SA levels were observed ($p<0.006$) (Table IV). It may be indicated that SA levels and blood glucose levels are linearly correlated. When the relationship between body mass index (BMI) and SA levels was examined it was found that in patients with BMI 29, the SA level was 44.59±4.9, and the SA level was 39.08±5.1 in patients with BMI 29 and below. There was no statistically significant difference between these two groups in terms of SA levels ($p=0.298$). There was no difference between the SA levels and age, gravida, parity, insulin intake, gestation week, delivery type, infant's gender, height, weight, APGAR score, neonatal care unit stay history and in terms of MPV, MCHC, MCH, PLT and bilirubin values in the neonatal blood ($p>0.005$) (Table V).

Table I: *Sialic acid level between diabetic patients and control group*

Patient group	n	Mean rank	*p*
Diabetic patient	48	46.94±3.1	0.155
Control	39	39.99±3.8	

Table II: *The relationship between sialic acid and diabetes type*

Diabetes type	n	Mean rank	*p*
Type I DM	4	46.25±3.6	
Type II DM	6	33.00±4.1	0.001
GDM	38	20.87±3.7	

DM: Diabetes mellitus, GDM: Gestational diabetes mellitus

Table III: *The relationship between diabetes regulation and sialic acid*

Diabetes regulation	n	Mean rank	*p*
Diet regulated	30	20.60±4.1	0.007
Insulin regulated	9	31.95±4.7	

Table IV: *The relationship between blood sugar level and sialic acid level*

Blood sugar	n	Mean rank	*p*
Normal	73	40.02±3.8	0.006
Higher	12	61.13±4.2	

Discussion

It is well known that SA levels increase in diabetic patients, cardiovascular diseases and many inflammatory conditions. There is a correlation between high blood glucose levels and SA levels in diabetic patients and there is a significant increase in SA levels in patients who develop diabetic complications. Also, high SA level is an indicator of coronary artery disease.

The adverse effects of uncontrolled diabetes on pregnancy and neonatal outcomes are well known. In this study, we evaluated the relationship between SA levels in the umbilical cord blood of the babies of diabetic versus non-diabetic patients and the neonatal outcomes. Despite the SA levels in the umbilical cord blood are higher in infants of diabetic mothers, the difference between SA levels and neonatal outcome in diabetic and non-diabetic mothers are not statistically significant (3,5,6).

Increased SA levels in pregnancy are due to physiological changes in organs and organ systems during pregnancy. The most important changes in pregnancy are observed in the circulatory system, the blood. Hence, in diabetic patients, there are significant changes in glycoprotein and cellular carbohydrate structures (7). A large proportion of SA in the body is found in the structure of fibrinogen, oromucoid, alpha-1 antitrypsin and haptoglobin (8). In addition as an acute phase reactant, fibrinogen levels increase 2-3 times in pregnancy.

Table V: *Comparison of demographic characteristics of diabetic and non-diabetic groups*

Demographic Feature	Diabetic (n=48)	Control (n=39)	*p*
Age	29±7	27±6	*p* >0.05
Gravida	3±1	3±1	*p* >0.05
Parite	2±2	2±1	*p* >0.05
Gestational week	38±3	38±4	*p* >0.05
Type of birth	NSVD	NSVD	*p* >0.05
	C/S	C/S	
Fetal gender	Male	Male	*p* >0.05
	Female	Female	
Lenght	1.52±12	1.55±9	*p* >0.05
Maternal weight	64±19	63±15	*p* >0.05
Fetal weight	3452±730	3320±540	*p* >0.05
APGAR score	1. minute: 8±2	1. minute: 8±1	*p* >0.05
	5. minute: 8±2	5. minute: 8±1	
Neonatal intensive care	Yes:2	Yes:1	*p* >0.05
	No:46	No:38	
MPV	9,6	9.2	*p* >0.05
MCH	27,9	28.1	*p* >0.05
MCHC	32,3	32.7	*p* >0.05
MCV	90,1	90.7	*p* >0.05
Bilirubin	1,9	2	*p* >0.05

MPV: Mean platelet volume, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, MCV: Mean corpuscular volume

When diabetic patients were grouped according to their diabetes type; serum SA levels of patients with type I diabetes were higher than those of types II diabetes and gestational diabetes. This may be due to the earlier onset of Type I diabetes and the earlier onset of renal and vascular complications of diabetes. Microangiopathic and macroangiopathic complications were higher in diabetic patients with higher SA levels. The underlying pathophysiology here is endothelial damage as SA contributes to the cell wall structure. Higher SA levels in the mother are also transferred to the fetus through the placenta. Therefore, in our study, the umbilical cord blood levels of SA in mothers with high blood glucose levels were also found to be high. From this, it can be postulated that umbilical cord SA levels may be accepted as an indirect indicator of blood glucose levels and glycemic control of the mother (3).

In a study comparing SA levels in gestational diabetes, impaired glucose tolerance test, and control groups, sialic acid level was found to be significantly high in patients with gestational diabetes and patients with impaired glucose tolerance test compared to the control group; and that it could be related with the inflammatory disorders in future (9). Sialic acid as an inflammatory indicator is effective in foreseeing Type II diabetes, gestational diabetes, and metabolic syndrome. In another study, gestational diabetes and control groups were compared and it was emphasized that there was a significant difference between sialic acid levels, that the high levels were associated with gestational diabetes and metabolic syndrome. Since the increased systemic inflammatory response was an early characteristic of metabolic syndrome, increased levels of sialic acid in gestational diabetes mellitus could be an early indicator of a potential metabolic syndrome in the future (10).

If blood glucose control in diabetic patients cannot be achieved by diet, it is necessary to switch to insulin therapy to prevent possible further complications. In our study, the SA levels in the umbilical cord blood of the pregnant women with their glycemic control are achieved by insulin was higher than that of the diet group. This may reflect the severity of diabetes.

In the study of Ycaoasyoolu et al. the relationship between perinatal asphyxia and serum SA level were evaluated and after 24 hours of neuronal damage, serum SA levels were found to be higher in asphyxia infants compared to the control group and proportional to the clinical severity (11). However, in our study, there was no relation between high SA levels and poor neonatal outcomes.

In normal pregnancies and in the postpartum period SA levels may be increased due to physiological changes in pregnancy. In their study, Crook et al evaluated the SA levels during pregnancy, postpartum period and nonpregnant women. In this study, it was shown that pregnant and postpartum patients had higher SA levels than the control group (12).

High SA levels in normal pregnants may not always reflect negative neonatal outcomes. Wu Y et al. suggested that high sialic acid levels in cord blood and colostrum may play an important role in the development of full-term infants' intelligence capacity (12,13). The SA levels in the cord blood reflect placental function as well since the placenta is rich in enzymes essential in SA metabolism.

In a study of Prajna et al. type II diabetes patients with and without nephropathy were compared and it was claimed that such microvascular complications as diabetic nephropathy were more frequently observed in patients with high total sialic acid level, and as a potential risk factor in the development of nephropathy. In another study, a high level of serum total SA was postulated to be a potential prognostic indicator of diabetic nephropathy (14,15).

It has already been known that obesity is associated with cardiovascular diseases and that the correlation of inflammation and insulin resistance increases the cardiovascular risk in these subjects. In a study evaluating the relationship between insulin sensitivity, insulin resistance and sialic acid levels in non-diabetic normotensive obese individuals, it was stated that insulin resistance, serum total, and protein-bound sialic acid levels significantly increased in the obese patients compared to the non-obese control group. Thus, sialic acid levels were higher in obese individuals and in these patients insulin resistance and decreased insulin sensitivity resulted in an increase in cardiovascular risk (10).

Although increased SA levels in non-pregnant diabetic patients have been reported as a significant indicator in terms of complications of diabetes, the early and late effects of the SA levels of cord blood in the babies of diabetic patients are not clear. The small number of patients in our study and the lack of long-term follow-up are limiting features.

In our study, no difference was found in the umbilical cord blood of the diabetic and non-diabetic patients in terms of SA levels and poor neonatal outcomes. However, more prospective controlled studies with a larger number of patients are needed to study the results of sialic acid levels and neonatal outcomes.

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