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Evaluation of Serum Paraoxonase Activity and Total Oxidant and Antioxidant Capacity in Infants of Diabetic Mothers

Diyabetik Anne Bebeklerinde Serum Paraoksonaz Aktivitesi ve Total Oksidan ve Antioksidan Kapasitenin Değerlendirilmesi

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Abstract

Background: This study aims to evaluate the paraoxonase (PON) activity, total oxidant (TOS) levels, and antioxidant capacities (TAS) in infants of diabetic mothers (IDM), to assess the risk of atherosclerosis formation.

Materials and Methods: A total of 58 infants born to mothers with pregestational or gestational diabetes who were followed up prospectively between 01.03.2012 and 25.09.2012 and were within the first 3 postnatal days were included in the study. Healthy infants without maternal risk factors were selected as the control group. The levels of PON, TOS, and TAS were compared between the groups.

Results: PON1 activity, TOS levels, and oxidative stress index were found to be significantly higher in IDM compared to the control group (p<0.01, p<0.01, p<0.01, respectively). However, no significant difference was found in serum TAS levels between the IDM and the control group (p=0.446).

Conclusions: Achieving glycemic control in diabetic mothers through intrauterine programming may reduce oxidative stress and the risk of atherosclerosis development by reducing the exposure of infants to hyperglycemia.

Keywords: Infant of diabetic mother, Serum paraoxonase activity, Oxidant-antioxidant system

Öz

Amaç: Bu çalışmada diyabetik anne bebeklerinde (DAB), ateroskleroz oluşma riskini gösteren Paraoksonaz (PON) aktivitesi ile total oksidan (TOS) ve antioksidan kapasitelerinin (TAS) değerlendirilmesi amaçlanmaktadır.

Materyal ve metod: Çalışmaya, prospektif olarak 01.03.2012-25.09.2012 tarihleri arasında, pregestasyonel veya gestasyonel diyabet nedeniyle izlenen 58 anneden doğan ve postnatal ilk 3 gün içinde olan yenidoğan bebekler dahil edilmiştir. Maternal risk faktörü olmayan sağlıklı bebekler kontrol grubu olarak alınmıştır. Hastaların PON, TOS ve TAS düzeyleri karşılaştırılmıştır.

Bulgular: DAB'de PON1 aktivitesi, TOS seviyeleri ve oksidatif stres indeksi kontrol grubuna göre anlamlı derecede yüksek bulunmuştur (sırasıyla; p<0,01, p<0,01, p<0,01). Serum TAS seviyelerinde ise kontrol grubuna göre anlamlı fark saptanmamıştır (p=0,446).

Sonuç: İntrauterin programlama ile diyabetik annelerin glisemik kontrolünün sağlanması, DAB'nin daha az hiperglisemiye maruz kalması durumunda oksidatif stresin azalabileceği düşündürmektedir.

Anahtar Kelimeler: Diyabetik anne bebeği, Serum paraoksonaz aktivitesi, Oksidan-antioksidan sistem

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Introduction

Metabolic disorders such as macrosomia and associated birth traumas, respiratory distress syndrome, transient tachypnea, hypertrophic cardiomyopathy, hyperbilirubinemia, polycythemia, renal vein thrombosis, congenital anomalies, as well as hypoglycemia, hypocalcemia, and hypomagnesemia, are frequently observed in infants of diabetic mothers (1). The fundamental mechanism underlying neuropathy development involves structural and functional impairments caused by hyperglycemia and related metabolic disturbances in various parts of the nervous system (2,3).

Gestational diabetes mellitus (GDM) poses significant risks not only to both mother and fetus during pregnancy (4) but is also linked to long-term health complications, including metabolic syndrome, type 2 diabetes mellitus (T2DM), and an increased risk of cardiovascular disease for both mothers and their offspring (4-6). Although the pathogenesis of GDM remains unclear, its onset and progression have been associated with genetic variants, elevated oxidative stress, and dyslipidemia (7-9).

Paraoxonase-1 (PON1) is a calcium-dependent enzyme, also known as aryldialkylphosphatase, synthesized in the liver and recognized for its antioxidant properties (10). PON1 is primarily associated with high-density lipoprotein cholesterol (HDL-C) in serum. Serum HDL-C concentrations are inversely correlated with atherosclerotic risk (11). Oxidative modifications of low-density lipoprotein cholesterol (LDL-C) play a critical role in the initiation and progression of atherosclerosis (12). While recent studies have proposed various mechanisms, HDL-C is known to protect LDL-C from oxidative modifications (13). This antioxidant capacity of HDL-C is largely attributed to PON1, with additional contributions from lecithin cholesterol acyltransferase (14). Studies have demonstrated that PON1 protects oxidized phospholipids on LDL-C from further oxidation (15). Notably, PON1 activity in neonates and premature infants is approximately half that of adults and reaches adult levels around one year after birth (16). The anti-atherogenic effects of PON1 stem from its ability to protect lipoprotein particles against free radical-induced oxidation (17).

The protective role of PON1 in atherosclerosis has been supported by various studies demonstrating both direct and indirect reductions of oxidative stress by this enzyme (15). Increased lipoprotein oxidation was reported in apolipoprotein E/PON1 double-mutant mice compared to apolipoprotein E mutant controls. Additionally, PON1 activity and its isoforms were reduced by 25-45% in apolipoprotein E deficient mice relative to controls (16). Subsequent research has shown decreased PON1 activity in individuals prone to atherosclerosis, including those with type 1 and type 2 diabetes or hypercholesterolemia. Assessing PON1 activity in children may thus be useful for early protection against future atherosclerosis (18).

Oxidative stress is broadly defined as the imbalance between the body's antioxidant defenses and free radical production, leading to lipid peroxidation of cellular membranes (19).

The aim of this study was to evaluate the relationship between serum PON1 activity and the oxidant-antioxidant system in infants of diabetic mothers.

Materials and Methods

Study Group

This prospective study, conducted between 01.03.2012 and 25.09.2012, included newborns within the first 72 hours of life who were admitted to or born in the neonatal unit, pediatric emergency, outpatient clinics, and gynecology and obstetrics services, born to mothers with pregestational or gestational diabetes, along with a healthy control group of infants born to non-diabetic mothers. Ethical approval was obtained from the Ethics Committee of Harran University Faculty of Medicine (approval no: 12/03/20, date: May 18, 2012) and written informed consent was secured from the legal guardians of all participants.

At enrollment, the following data were recorded: maternal age, paternal age, infant gender, height, weight, head circumference, infant age, number of maternal pregnancies, type of maternal diabetes mellitus, results of the Oral Glucose Tolerance Test (OGTT) for gestational diabetes mellitus, maternal treatment during pregnancy, and maternal hemoglobin A1c levels.

The control group consisted of healthy newborns born to mothers without any known health risks before or during pregnancy. These infants were free from any complaints or disease based on history and physical examination, were of the same postnatal age, and were neither premature nor of low birth weight.

Inclusion Criteria

1. Term infants (gestational age 38-42 weeks)
2. Birth weight ≥2,500 grams
3. Age within the first 72 hours postnatally
4. Mothers diagnosed with diabetes mellitus but without other systemic diseases
5. Apgar score ≥8 at 1 and 5 minutes after birth

Exclusion Criteria

1. Preterm infants or those with birth weight <2,500 grams
2. Infants with septicemia, dehydration, pulmonary disease, hypoxia/anoxia, congenital or chromosomal anomalies, metabolic diseases, cephalohematoma, ecchymosis, systemic diseases, infections, or other clinical conditions potentially causing increased free radical formation.

Biochemical Analysis

Plasma paraoxonase/arylesterase activity, HDL, LDL, total antioxidant status (TAS), and total oxidant status (TOS) levels were measured using serum samples collected in gel tubes. Peripheral venous blood samples were centrifuged at 3,500 rpm for 10 minutes, and serum was aliquoted into Eppendorf tubes, then stored at -80 °C until analysis. On the day of analysis, samples from both patient and control groups were thawed to room temperature and analyzed simultaneously in a single batch.

Measurement of Total Antioxidant Status (TAS):

TAS was determined based on the reduction of the colored ABTS cationic radical by antioxidants in the sample. The degree of decolorization correlates with the total antioxidant concentration. Trolox, a water-soluble vitamin E analog, was used as a calibrator. Results were expressed as mmol Trolox equivalents per liter (mmol Trolox Eqiv/L).

Measurement of Total Oxidant Status (TOS):

TOS was measured colorimetrically based on the oxidation of ferrous ions to ferric ions by oxidant molecules in the samples. Hydrogen peroxide was used as the calibrator. Results were reported as micromoles of H_2O_2 equivalents per liter (µmol H_2O_2 Eqiv/L).

Oxidative Stress Index (OSI):

OSI was calculated as the ratio of TOS to TAS levels and expressed in arbitrary units.

Measurement of Paraoxonase Activity:

PON enzyme activity was assessed using paraoxon (0,0-diethyl-0-p-nitrophenyl phosphate) as the substrate and arylesterase activity was measured using phenyl acetate as substrate. For PON activity measurement, 100 mM Tris-HCl buffer with pH=8 containing 5 mM $CaCl_2$ and 7 mM paraoxon was used and considered as Reagent 1 (R1). 220µL of reagent 1 was taken 10 µL from the sample volume and applied to the abbott aeroset autoanalyzer. The minute absorbance at 412 nm of p-nitrophenol formed by enzymatic hydrolysis of PON was recorded. Molar absorption coefficient 18,290 (ε) was taken and 1 unit for activity was calculated as 1 micromol p-nitrophenol/ml serum/min.

Measurement of Arylesterase Activity:

Arylesterase activity was determined using phenyl acetate as the substrate. The reaction mixture contained 100 mM Tris-HCl buffer (pH 8.0) with 2 mM CaCl2 and 13 mM phenyl acetate. The phenol formed during enzymatic hydrolysis was measured at 270 nm using a Jasco V-530 UV/VIS spectrophotometer. The molar absorption coefficient was 1.310 $M^{-1} \cdot cm^{-1}$ and activity was expressed in U/L, where 1 U corresponds to 1 µmol of phenol formed per mL of serum per minute.

Serum total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglyceride levels were measured using colorimetric methods. Serum VLDL-C levels were calculated accordingly.

Statistical Analyses

Statistical analysis was performed using SPSS version 11.5 (SPSS Inc., Chicago, IL, USA). Data were expressed as mean ± standard deviation (SD). The Kolmogorov-Smirnov test was used to assess the normality of the data distribution. Differences between groups were analyzed using the Student's t-test or the Mann-Whitney U test, as appropriate. Categorical variables were compared using the chi-square test. A p-value <0.05 was considered statistically significant.

Results

Between March 1, 2012, and September 25, 2012, a total of 58 infants of diabetic mothers (IDMs) and 45 healthy newborns were included in the study. All participants were evaluated within the first 72 hours of life.

The mean birth weight was significantly higher in the IDM group (3713.17±460.89 g) compared to controls (2956.77±184.48 g, p<0.001). The mean gestational age was slightly lower in the IDM group (37.82±0.92 weeks) compared to the control group (38.20±0.75 weeks), with a statistically significant difference (p=0.03). Maternal age was also significantly higher in the IDM group (p<0.01), while gender distribution was similar between the two groups. The mean HbA1c level of diabetic mothers was 6.05±0.87%. Demographic data are presented in Table 1.

Table 1. Demographic and clinical characteristics of ınfants of diabetic mothers and control group

Variable	Infants of diabetic mothers (n=58)	Control group (n=45)	P value
Maternal age (years)	33.37±5.73	28.26±4.52	<0.01
Infant gender (female/male)	27/31	21/24	0.99
Infant age (days)	1.17±0.50	1.04±0.29	0.132
Height (cm)	50.12±1.35	50.02±0.89	0.674
Birth weight (grams)	3713.17±460.89	2956.77±184.48	<0.001

Table 1. Continued			
Maternal HbA1c (%)	6.04±0.81	-	-
Gestational age (weeks)	37.82±0.92	38.20±0.75	0.03
Mode of delivery (NVY/C/S)	5/53	7/38	0.277
Diabetes type (T1/T2/GDM)	7/7/44	0/0/0	-
Head circumference (cm)	35.79±0.64	35.87±0.33	0.636
Number of maternal pregnancies	5.32 ± 2.62	3.11±2.0	0.018
OGTT 0-hour (mg/dL)	122.04±26.06	88.0±9.97	<0.0001
OGTT 1-hour (mg/dL)	205.11±39.56	-	-
OGTT 2-hour (mg/dL)	167.95±25.97	-	-
Data are presented as mean ± standard deviation (mean ± SD) HbA1c: Hemoglobin A1c, OGTT: Oral Glucose Tolerance Test, NVY: Normal vaginal delivery, C/S: Cesarean section, T1: Type 1 diabetes, T2: Type 2 diabetes, GDM: Gestational diabetes mellitus			

Biochemical analysis revealed the following:

- Paraoxonase-1 (PON1) activity was significantly lower in the IDM group than in the control group (44.77±13.69 U/L vs. 57.39±18.23 U/L, p<0.01).
- Arylesterase (AREST) activity showed no significant difference between groups (58.58±14.34 U/L vs. 60.19±9.68 U/L, p=0.53).
- Total Antioxidant Status (TAS) levels were similar in both groups (0.97±0.08 vs. 0.98±0.07 mmol Trolox Eq./L, p=0.44).
- Total Oxidant Status (TOS) levels were significantly higher in the IDM group (27.05± 8.89 vs. 19.76±3.61 µmol H_2O_2 Eq./L, p<0.001).
- Oxidative Stress Index (OSI) was also significantly elevated in the IDM group (2.79±0.90 vs. 2.01±0.39 Arbitrary Units, p<0.001).

Lipid profile comparisons showed:

- Triglyceride (TG) levels were significantly higher in the IDM group (77.40 ± 54.07 vs. 43.55±35.76 mg/dL, p=0.005).
- VLDL levels were also elevated in the IDM group (15.47±10.82 vs. 8.7±7.15 mg/dL, p=0.04).
- Total cholesterol (CHOL) and LDL levels were slightly higher in the IDM group, but the differences were not statistically significant (CHOL: 77.40±33.97 vs. 66.93±19.0 mg/dL, p=0.13; LDL: 36.13±24.07 vs. 33.66±14.37 mg/dL, p=0.62).
- HDL levels were similar between the groups (25.80±10.64 vs. 24.55±6.98 mg/dL, p=0.58).

These findings are summarized in Table 2.

Table 2. Oxidative stress, PON, arylesterase, triglyceride, cholesterol, HDL, LDL, and VLDL levels in infants of diabetic mothers and control group

Variable	Infants of diabetic mothers (n=58)	Control group (n=45)	p-value
TAS (mmol Trolox Eq./L)	0.97±0.08	0.98±0.07	0.446
TOS (µmol H_2O_2 Eq./L)	27.05±8.89	19.76±3.61	<0.01
OSI (Arbitrary Unit)	2.79±0.90	2.01±0.39	<0.01
PON1 (U/L)	44.77±13.69	57.39±18.23	<0.01
AREST (U/L)	58.58±14.34	60.19±9.68	0.53
TG (mg/dL)	77.40±54.07	43.55±35.76	0.005
CHOL (mg/dL)	77.40±33.97	66.93±19.00	0.13
HDL (mg/dL)	25.80±10.64	24.55±6.98	0.58
LDL (mg/dL)	36.13±24.07	33.66±14.37	0.62
VLDL (mg/dL)	15.47±10.82	8.70±7.15	0.04
Data are presented as mean ± standard deviation (mean ± SD) TAS: Total antioxidant status, mmol/L, µmol/L, TOS: Total oxidant status, mmol/L, µmol/L, OSI: Oxidative Stress Index, PON1: Paraoxonase 1, AREST: Arylesterase, TG: Triglyceride, CHOL: Cholesterol, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, VLDL: Very Low-density lipoprotein			

Discussion

Pregnancy is a physiologically stressful condition and has been associated with an atherogenic lipid profile and increased oxidative stress in women (20). Compared to healthy pregnancies, women with GDM exhibit more severe oxidative stress and a more impaired glycolipid metabolism profile (9). Similar patterns are observed in neonates born to mothers with

GDM, including elevated fasting glucose, insulin, 8-isoprostane, xanthine oxidase, and malondialdehyde levels. Meanwhile, total antioxidant capacity and antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) are significantly reduced in these neonates compared to controls (21).

In the present study, we found that TOS and OSI levels were significantly higher, while PON1 activity was significantly lower in infants of diabetic mothers compared to healthy controls. Additionally, serum triglyceride levels were elevated in the IDM group. These findings suggest that infants born to diabetic mothers are exposed to a more pro-oxidative intrauterine environment, leading to redox imbalance and a more unfavorable lipid profile, which may predispose them to metabolic and cardiovascular complications later in life.

In diabetes, the most commonly observed lipid abnormality is hypertriglyceridemia accompanied by reduced HDL levels. In type 1 diabetes, although total lipid levels may appear normal, increased glycation and oxidation of lipoproteins impair their function (22). The antioxidant role of HDL is also diminished, likely due to reduced PON1 activity, which is crucial for HDL's protective effect against lipid peroxidation. In our study, although HDL levels did not significantly differ between groups, triglyceride and VLDL levels were significantly elevated in the IDM group, aligning with the typical diabetic dyslipidemia profile.

Over the past ten years, there has been a notable increase in the incidence of cardiovascular diseases in children, with contributing factors including family history, obesity, hypertension, smoking, and abnormal lipid levels (23). The oxidative modification of LDL is a key event in the initiation and progression of atherosclerosis (24). Antioxidants such as SOD, catalase, GSH-Px, and vitamin E help protect LDL from oxidative damage and reduce the risk of atherosclerotic lesion development (25). Among these protective mechanisms, PON1 plays a critical role by preventing oxidative modifications of serum lipoproteins (26). Mackness et al. (26) demonstrated that PON1 accumulates in the arterial wall during atherogenesis, where it prevents LDL oxidation. Low PON1 activity has been linked to an increased risk of atherosclerosis and cardiovascular disease in various studies (27).

PON1 activity is closely associated with HDL levels in serum. Although the nature of this relationship is not fully understood, increased PON1 activity is generally observed alongside higher HDL levels (28). PON1 is thought to offer anti-atherogenic protection by inhibiting lipoprotein oxidation (29).

Several studies support our findings. Mackness et al. (30) found significantly reduced PON1 activity in diabetic patients compared to healthy controls. Similarly, Parmaksız et al. (31) reported lower PON1 activity in a streptozotocin-induced diabetic rat model. These results support the idea that hyperglycemia reduces PON1 activity, consistent with our findings ($p<0.001$).

Numerous studies have shown that reduced PON and arylesterase activities are associated with various diseases that are also risk factors for atherosclerosis (32-36). For example, McElveen et al. (32) reported significantly lower PON1 activity in patients with acute myocardial infarction, and Mackness et al. (33) found similar results in patients with coronary artery disease. A Japanese study further identified PON1 as an independent risk factor for coronary artery disease (34). In a rat study by Thomas Moya et al. (35), a 40% caloric restriction significantly decreased PON1 activity, which correlated with apolipoproteins Apo-J and Apo-A1-especially in female rats-indicating potential sex-related differences in PON1 activity. Additionally, Çakmak et al. (36) observed increased oxidative stress and decreased PON1 activity in pediatric patients with beta-thalassemia major, suggesting an elevated atherosclerotic risk in these patients.

Oxidative stress plays a central role in the development of many diseases. Given that antioxidant therapies can reduce oxidative damage, they may offer potential treatment avenues for oxidative stress-related conditions. In the context of diabetes, targeting oxidative stress could present a novel therapeutic strategy to mitigate disease complications.

This study has some limitations. Notably, we did not perform mid- or long-term follow-up of the infants regarding lipid metabolism or subclinical atherosclerosis. Furthermore, anthropometric and metabolic markers were not assessed over time. Information on the duration and severity of maternal diabetes, including the presence of end-organ damage, was also limited.

Conclusion

In this study, infants of diabetic mothers exhibited significantly higher TOS and OSI levels and lower PON1 activity compared to healthy controls, indicating an increased state of oxidative stress. These findings suggest that poor maternal glycemic control may contribute to oxidative imbalance in the intrauterine environment, thereby reducing PON1 activity and potentially increasing the risk of atherosclerosis in these infants.

Optimizing maternal glycemic control during pregnancy may help reduce fetal exposure to hyperglycemia and associated oxidative stress. In turn, this may support the preservation of antioxidant defense mechanisms such as PON1 activity and lower the long-term risk of atherosclerosis in infants of diabetic mothers.

Ethical Approval: *This study was approved by the Ethics Committee of Harran University Faculty of Medicine (approval no: 12/03/20, date: May 18, 2012).*
Author Contributions:
Concept: S.G., M.K., A.Ç.
Literature Review: S.G., M.K., A.Ç.
Design: S.G., M.K., A.Ç.
Data acquisition: S.G., M.K.
Analysis and interpretation: S.G., M.K.
Writing manuscript: S.G., M.K.
Critical revision of manuscript: S.G., A.Ç.
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