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Serum paraoxonase and arylesterase activities in iron deficiency anemia during pregnancy

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Aim: To investigate serum paraoxonase and arylesterase activities, and lipid hydroperoxide levels in pregnant women with iron deficiency anemia.

Materials and methods: Paraoxonase and arylesterase activities, and lipid hydroperoxide levels were assessed for pregnant women with iron deficiency anemia (n = 50) and controls (n = 70). Serum basal and salt-stimulated paraoxonase, and arylesterase activities were measured spectrophotometrically. The lipid hydroperoxide levels were measured by ferrous ion oxidation xylenol orange assay. In addition, lipid parameters were determined by routine laboratory methods.

Results: Basal and salt-stimulated paraoxonase, and arylesterase activities were significantly lower (P = 0.026, P = 0.031, and P = 0.018, respectively) in pregnant women with iron deficiency anemia when compared to the controls, while lipid hydroperoxide levels were significantly higher (P = 0.004). A significant positive correlation was found between paraoxonase activity and hemoglobin levels (r = 0.329, P = 0.020), while there was inverse correlation between lipid hydroperoxide and hemoglobin levels (r = -0.457, P = 0.001). Among iron deficiency anemia, serum paraoxonase activity was inversely correlated with lipid hydroperoxide levels (r = -0.535, P < 0.001).

Conclusion: The findings of the present study have shown that diminished serum paraoxonase and arylesterase activities, and increased lipid hydroperoxide levels may play a role in the early pathogenesis of atherosclerotic heart disease in pregnant women with iron deficiency anemia.

Key words: Iron deficiency anemia, pregnancy, paraoxonase, arylesterase, lipid hydroperoxide levels

Gebelikte demir eksikliği anemisinde serum paraoksanaz ve arilesteraz aktiviteleri

Amaç: Demir eksikliği anemisi olan gebe kadınlarda serum paraoksanaz ve arilesteraz aktiviteleri ve lipit hidroperoksit seviyelerini araştırmaktır.

Yöntem ve gereç: Paraoksanaz ve arilesteraz aktiviteleri ve lipit hidroperoksit seviyeleri demir eksikliği anemisi olan (n = 50) ve olmayan (n = 70) gebe kadınlarda değerlendirildi. Serum bazal ve tuz paraoksanaz ve arilesteraz aktiviteleri spektrofotometrik olarak ölçüldü. Lipit hidroperoksit seviyeleri xylenol orange mevcudiyetinde demir iyon oksidasyonuyla ölçüldü. Lipit profili ise rutin laboratuar yöntemleriyle çalışıldı.

Bulgular: Bazal ve tuz ile uyarılan paraoksanaz ve arilesteraz aktiviteleri kontrol ile karşılaştırıldığında demir eksikliği anemisi bulunan gebelerde anlamlı derecede azalmasına rağmen (sırasıyla, P = 0,026, P = 0,031, ve P = 0,018), lipit hidroperoksit seviyeleri anlamlı derecede yüksek bulundu (P = 0,004). Hemoglobin seviyesi ve lipit hidroperoksit seviyeleri arasında negatif korelasyon varken (r = -0,457, P = 0,001), paraoksanaz aktivitesi ve hemoglobin düzeyi arasında pozitif korelasyon bulundu (r = 0,329, P = 0,020). Demir eksikliği anemisi bulunan gebelerde, serum paraoksanaz aktivitesi lipit hidroperoksit seviyeleri ile negatif korelasyona sahipti (r = -0,535, P < 0,001).

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Sonuç: Bu çalışmanın bulguları, azalmış serum paraoksanaz ve arilesteraz seviyeleri ve artmış lipit hidroperoksit düzeylerinin, demir eksikliği anemisi bulunan gebe kadınlarda aterosklerotik kalp hastalığının erken patogenezinde bir rol oynayabileceğini göstermiştir.

Anahtar sözcükler: Demir eksikliği anemisi, gebelik, paraoksanaz, arilesteraz, lipid hidroperoksid

Introduction

Anemia incidence during pregnancy is increasing, especially in industrialized and developing countries. Iron deficiency is the most common cause of anemia during pregnancy (1) and affects the production of a group of proteins containing Fe^{2+}, such as cytochromes, myoglobin, catalase, and peroxidase (2). Additionally, iron deficiency anemia (IDA) during pregnancy is associated with adverse pregnancy outcomes, such as preterm birth, low birth weight, and increased maternal mortality (3). There are also several studies that show behavioral defects in both human (4) and animal infants (5). Increased oxidative stress and decreased antioxidative status in IDA have been revealed by many authors (6).

Lipid hydroperoxide (LOOH) is a well-known marker of oxidative stress formed from unsaturated phospholipids, glycolipids, and cholesterol by peroxidative reactions under oxidative stress (7). Oxidized low-density lipoprotein (LDL), besides membrane-bound cholesterol-derived hydroperoxides, is the main form of LOOH responsible for the development of oxidative stress-related atherosclerosis, and adverse cardiovascular events (7).

Oxidative stress plays a crucial role in the development of atherosclerosis through the oxidation of LDL that subsequently leads to the formation of foam cells (8). Conversely, high-density lipoprotein (HDL) is a well-known anti-oxidant that prevents atherosclerosis (9). The pathogenesis of atherosclerosis is complex and multifactorial. Even though the major risk factors of atherosclerosis are lipid disorders, hypertension, smoking, and diabetes mellitus, these major risk factors for atherosclerosis explain only 50% of its etiology. Therefore, looking for new risk factors of atherosclerosis is necessary (10).

Paraoxonase 1 (PON1) plays a key role in protecting LDL and HDL from oxidation by hydrolyzing activated phospholipids, (11) and lipid peroxide products (12). Through these activities, serum PON1 plays an important role in the prevention of atherosclerosis (11). Further evidence for the protective role of PON1, includes studies that show decreased PON1 activity in subjects who have had coronary artery disease (13), hypercholesterolemia, type 2 diabetes (14), and in subjects with IDA (2).

To the best of our knowledge, PON1 and arylesterase activities in pregnant women with IDA have not been evaluated. In addition, it is still unknown whether there is any relationship between PON1 activity and subclinical atherosclerosis in pregnant women with IDA. The purpose of this study was to evaluate the PON1 and arylesterase activities as antioxidants and the LOOH levels as an oxidative stress indicator in pregnancies with IDA.

Materials and methods

Study population

This study was conducted at the Departments of Obstetrics, Gynecology, and Clinical Biochemistry at Harran University and Şanlıurfa Maternity and Women's Health Hospital between 1 August 2007 and 31 June 2008. Informed consent for participation in the study was obtained from all women. The study protocol conforms to the principles of the Helsinki Declaration, and was approved by the Medical Ethics Committee of Harran University.

Eligible participants were pregnant women, between the 24th and 32nd week of gestation, with established IDA as defined by the following parameters: hemoglobin (Hb) < 11 g/dL, mean corpuscular volume (MCV) < 80 fL, and serum ferritin < 12 g/L. Fifty pregnant subjects with IDA and 70 healthy pregnant controls were enrolled in the study. The control group was selected according to the following criteria: Hb > 11 g/L, MCV > 80 fL and

ferritin > 12 g/L. We used C-reactive protein (CRP) as an indicator of immune system activation. A CRP value > 5.0 mg/L was an exclusion criterion since serum ferritin levels can be falsely elevated during inflammation. In order to exclude the presence of thalassemia trait, subjects with MCV < 80 fL underwent Hb electrophoresis. Only 2 patients were excluded from the study, due to thalassemia trait. Stool examinations for parasites were performed in all enrolled women. Patients and controls were matched based on gestational age, parity, maternal age, and body mass index. Gestational age was calculated from the last menstrual period and confirmed by a routine ultrasound.

All participants were of low socioeconomic status. They were visiting a physician for the first time, and so they were not taking iron and vitamin supplements. Exclusion criteria for all study participants included: smoking, alcohol intake, preeclampsia, multiple gestations, diabetes mellitus, rheumatoid arthritis, malignancy, myoma uteri, systemic or local infection, acute-chronic liver diseases, renal dysfunction, history of hematological disease, anemias other than IDA, and the prensence of gastrointestinal or other parasitic diseases.

Blood sample collection

Blood samples were obtained in the morning from the cubital vein after an overnight fast. Samples were drawn from the cubital vein into blood tubes, and were immediately separated from the cells by centrifugation at 3000 × *g* for 10 min, stored on at -70 °C, and then analyzed. The blood samples were collected only for the purpose of this study.

Measurement of paraoxonase and arylesterase activities

PON1 and arylesterase activities were measured using commercially avaliable kits (Relassay®, Turkey). PON1 activity measurements were performed, both in the absence and presence of NaCl (salt-stimulated activity) (15). The rate of paraoxon hydrolysis (diethyl-*p*-nitrophenylphosphate) was measured by monitoring the increase of absorption at 412 nm at 37 °C. The amount of generated *p*-nitrophenol was calculated from the molar absorption coefficient at pH 8.5, which was 18.290 M^{-1} cm^{-1} (15). PON1 activity was expressed as U/L serum. Phenylacetate was used as a substrate to measure the arylesterase activity. Enzymatic activity was calculated from the molar absorption coefficient of the produced phenol, 1310 M^{-1} cm^{-1}. One unit of arylesterase activity was defined as 1 μmol phenol generated per minute under the above conditions and expressed as U/L (16). PON1 phenotype distribution was determined by a double substrate method, which calculates the ratio of salt-stimulated PON1 activity to arylesterase activity (15).

Measurement of lipid hydroperoxide levels

Serum LOOH levels were measured by the ferrous ion oxidation-xylenol orange (FOX-2) method described previously (17). The levels of triglycerides (TG), total cholesterol (TC), HDL-cholesterol (HDL-C), LDL-cholesterol (LDL-C), and fasting glucose were determined using commercially available assay kits (Abbott®, Illinois, USA) with an Abbott Aeroset auto-analyzer (Abbott, Illinois, USA). A complete blood count was performed using Celdyne 3700 Haematology Analyzer (Abbott). Serum ferritin was measured using an automated chemiluminescence autoanalyzer (Roche®, Basel, Switzerland).

Statistical analysis

All analyses were conducted using SPSS 11.5 (SPSS for Windows 11.5, Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation (S.D.). Parameter comparisons were performed using the Student's t-test. Pearson correlation tests were used for correlation analyses. For all statistical analysis, $P < 0.05$ was considered as significant.

Results

Demographic and clinical data for all subjects are summarized in Table 1. There were no significant differences between women with IDA and the controls with respect to maternal age, gestational age, parity, and body mass index (BMI).

While TC levels were similar in the IDA and control groups ($P = 0.136$), TG and LDL-C levels were significantly higher in women with IDA ($P = 0.024$ and $P = 0.016$, respectively) as compared to levels in the control group. In contrast, HDL-C, hemoglobin, and ferritin levels were significantly lower in women

Table 1. Demographic and clinical parameters for patients with iron deficiency anemia (IDA) and the controls. Values are presented as mean ± S.D.

Parameters	IDA (n = 50)	Controls (n = 70)	P value
Age (y)	28.7 ± 6.1	27.9 ± 5.8	0.499
Body mass index (kg/m^2)	27.2 ± 3.9	26.6 ± 3.7	0.403
Gestational age (weeks)	28.8 ± 2.7	28.1 ± 2.4	0.161
Parity	2.4 ± 2.1	2.1 ± 1.7	0.402
Hemoglobin (g/dL)	9.6 ± 0.4	12.8 ± 0.6	< 0.001
Hemotocrit (%)	31.3 ± 1.4	37.1 ± 2.7	< 0.001
Mean corpuscular volume (fL)	71.5 ± 2.4	88.0 ± 4.7	< 0.001
Ferritin (g/L)	3.8 ± 1.6	24.4 ± 16.5	< 0.001
Total cholesterol (mg/dL)	203 ± 47	184 ± 56	0.136
Triglyceride (mg/dL)	180 ± 78	138 ± 82	0.024
LDL-C (mg/dL)	144 ± 26	127 ± 43	0.016
HDL-C (mg/dL)	34.1 ± 8.9	38.2 ± 7.5	0.008

Abbreviations

HDL-C: high-density lipoprotein-cholesterol
LDL-C: low-density lipoprotein-cholesterol

with IDA (P = 0.008, P < 0.001, and P < 0.001, respectively) (Table 1).

Basal and salt-stimulated PON1, and arylesterase activities were significantly lower in women with IDA when compared to the controls (P = 0.026, P = 0.031, and P = 0.018, respectively), while LOOH levels were significantly higher in the cases than in the controls (P = 0.004). Additionally, there was no statistically significant difference between the PON1/HDL-C ratios of the groups (P = 0.298) (Table 2).

In patients with IDA, PON1 activity was positively correlated with HDL-C levels (r = 0.344, P = 0.014), while LDL-C levels were inversely correlated (r = -0.467, P = 0.001) (Table 3). Additionally, LOOH levels were inversely correlated with PON1 activity (r = -0.535, P < 0.001), but it was positively correlated with LDL-C levels (r = 0.371, P = 0.008) (Table 3).

Interestingly, hemoglobin and ferritin levels were significantly correlated with PON1 activity (r = 0.329, P = 0.020; and r = 0.599, P < 0.001, respectively)

Table 2. Lipid hydroperoxide, basal/salt-stimulated paraoxonase activities and arylesterase activity in pregnant women with iron deficiency anemia (IDA) and the controls. Values are presented as mean ± S.D.

Parameters	IDA (n = 55)	Controls (n = 59)	P value
Basal paraoxonase (U/L)	199 ± 82	238 ± 99	0.026
Salt-stimulated paraoxonase (U/L)	495 ± 365	666 ± 459	0.031
Arylesterase (kU/L)	166 ± 34	181 ± 31	0.018
LOOH (μmol H_2O_2 Eqv./L)	11.1 ± 2.2	9.9 ± 2.0	0.004
Paraoxonase/HDL-C ratio	6.1 ± 2.4	6.7 ± 3.8	0.298

Abbreviations

LOOH: lipid hydroperoxide
HDL-C: high-density lipoprotein-cholesterol

Table 3. Correlations between paraoxonase activity, arylesterase activity, LOOH, HDL-C, LDL-C, Hb, Hct, MCV, and ferritin levels in pregnant women with iron deficiency anemia.

	B-PON	Arylesterase	LOOH	HDL-C	LDL-C	Ferritin	Hb	MCV
SS-PON								
r	0.970	0.178	-0.515	0.361	-0.490	0.643	0.361	0.338
P	<0.001	0.217	<0.001	0.010	<0.001	<0.001	0.010	0.016
B-PON								
r		0.366	-0.535	0.344	-0.467	0.599	0.329	0.315
P		0.009	<0.001	0.014	0.001	<0.001	0.020	0.026
Arylesterase								
r			-0.237	0.090	-0.153	0.102	0.034	0.028
P			0.098	0.536	0.288	0.483	0.816	0.846
LOOH								
r				-0.369	0.371	-0.470	-0.457	-0.173
P				0.008	0.008	0.001	0.001	0.230
HDL-C								
r					-0.222	0.437	0.286	0.197
P					0.122	0.001	0.044	0.171
LDL-C								
r						-0.385	-0.172	-0.376
P						0.006	0.232	0.007
Ferritin								
r							0.661	0.372
P							<0.001	0.008
Hb								
r								0.300
P								0.034

Abbreviations

SS-PON: salt-stimulated paraoxonase
B-PON: basal paraoxonase
HDL-C: high-density lipoprotein cholesterol
LDL-C: low-density lipoprotein cholesterol
LOOH: lipid hydroperoxide
Hb: hemoglobin
Hct: hemotocrit
MCV: mean corpuscular volume.

(Figure), and LOOH levels (r = -0.457, P = 0.001; and r = -0.470, P = 0.001, respectively) in pregnant patients with IDA.

Discussion

In the current study, we found that basal and salt-stimulated PON1 activities and arylesterase activity were significantly lower in pregnant subjects with IDA than in the healthy pregnant controls. In contrast, LOOH levels were significantly higher in pregnant subjects with IDA. To our knowledge, this is the first paper reporting on the PON1 and arylesterase activities in pregnant women with IDA. A search of MEDLINE (English language; 1966–July 2008; search terms: "PON1" and "arylesterase" and "pregnancy"

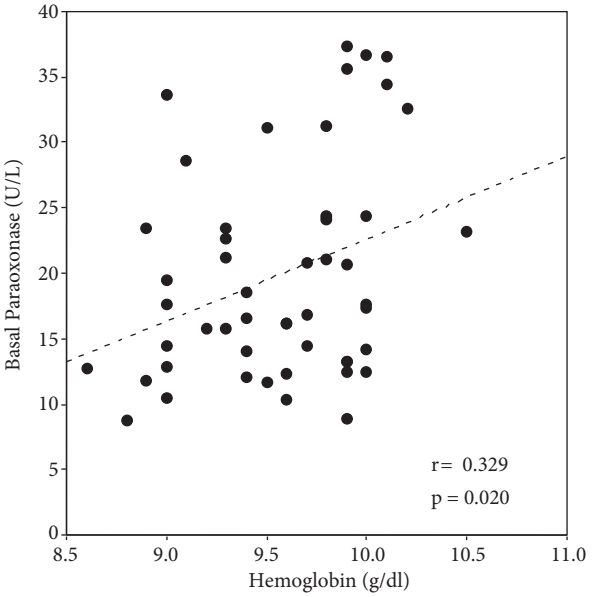

Figure. There was a statistically significant correlation between paraoxonase activity and hemoglobin levels.

and "IDA") revealed no other cases; however, a study by Aslan et al. shows that PON1 activity is lower in non-pregnant subjects with IDA than in the controls (2).

According to our data, increased LOOH levels and decreased PON1 activity contribute to oxidative stress in pregnant women with IDA. In addition, it appears that decreased PON1 and arylesterase activities may also play a role in the pathogenesis of subclinical atherosclerosis in pregnant women with IDA by increasing the susceptibility to lipid peroxidation.

In several studies, oxidants levels and antioxidant enzyme activity have been evaluated in patients with IDA (18). Although conflicting results have been reported (19), it is generally accepted that oxidative stress is increased through an increase in oxidant levels and/or decrease in antioxidant enzyme capacities in IDA. In the present study, we observed that LOOH levels increased in pregnant women with IDA. This finding was consistent with previous reports with respect to increased oxidative stress.

Aviram et al. (12) have reported that HDL protects LDL against oxidative modification, which is thought to be central to the initiation and progression of atherosclerosis. It is well known, from epidemiological data, that HDL exerts cardioprotective properties through its anti-oxidant activity, which is largely maintained by PON1 (20). It has been reported that PON1 protects lipoproteins against oxidative modification (21). Furthermore, the association between PON activity and the development of atherosclerosis was elucidated in previous animal and human studies. HDL isolated from PON-deficient mice was unable to protect LDL from oxidation. Additionally, PON-deficient mice developed more aortic atherosclerotic lesions with atherogenic diet than wild-type mice (22), whereas mice that overexpressed human PON1 were resistant to atherosclerosis (23). Moreover, human epidemiological studies have revealed an association between decreased PON1 levels and an increased risk for atherosclerosis (24). In a recent study Merono et al. studied proatherogenic disturbances in IDA, and revealed diminished levels of PON1 activity, which was accepted to represent proatherogenic state (25).

Interestingly, in the present study, there was a significant correlation between PON1 activity and the degree of anemia. The mechanism behind this association is unknown. It is possible that the pathogenesis of decreased hemoglobin may also play a role in the reduction of PON1 activity. Additionally, in our study, PON1/HDL ratios were not significantly different between groups, which would implicate that PON1 and HDL values are not independent from each other.

In conclusion, we found significantly lower levels of PON1 activity and significantly higher LOOH levels in pregnant women with IDA. This evidence supports the hypothesis that decreased PON1 activity is associated with the increased lipid peroxidation and decreased HDL concentration found in IDA. Our findings suggest that a decrease in the activity of PON1 and increased LOOH levels may play a role in the early pathogenesis of atherosclerotic heart disease in pregnant women with IDA. However, long-term clinical studies are needed to clarify the pathophysiological role of serum PON1 activity in IDA.

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