

Research Article



Assessment of the Relationship between Myeloperoxidase and Paraoxonase Levels in Prediction of Preeclampsia.

Yahya Y. Z. Fareed¹, Basima Sh. AL-Ghazali², Husham K. Mankhi^{3*}

¹Al-Nahrain university, College of Medicine, Baghdad, Iraq.

²Al-Kufa university, College of Medicine, Baghdad, Iraq.

³Al-Kufa university, College of Pharmacy, Baghdad, Iraq.

*Corresponding author's E-mail: haider_bahaa@yahoo.com

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ABSTRACT

The objective of present study was to assess the relationship of levels of myeloperoxidase and paraoxonase in prediction of preeclampsia. Two hundred and ten blood samples were collected from patients. Twenty seven patients were developed PE. These patients were followed for up to five months (first reading at 16-20 week, second reading at 21-28 week and third reading at 29-40 week). Patients suffered from any other disease were not included in the current study. The control group consisted of one hundred and eighty subjects. They were pregnant women without preeclampsia and other complications. These patients also were followed for up to five months (first reading at 16-20 week, second reading at 21-28 week and third reading at 29-40 week). Three patients were escaped. Compared with the control, levels of serum MPO was increased and PON-1 was decreased when compared preeclamptic patients with the non-preeclamptic group ($P < 0.001$). There was a significant differences in third reading (29-40 week) of serum MPO and PON levels ($p \leq 0.001$) and second reading (21-28 week) of serum MPO and PON levels ($p \leq 0.001$) when compared to first reading (16-20 week) of serum levels of MPO and PON in the preeclamptic patients. No Significant correlations were observed for the levels of serum MPO and PON with ages, BMI and parity while significant correlations were observed for the levels of serum MPO with MAP of the preeclamptic and Non-preeclamptic group ($p < 0.001$) and significant negative correlations was observed for level of PON-1 with MAP.

Keywords: myeloperoxidase, paraoxonase, preeclampsia.

INTRODUCTION

Preeclampsia (PE), a human-pregnancy-specific disease defined as the occurrence of hypertension and significant proteinuria in a previously healthy woman on or after the 20th week of gestation, occurs in about 8-12% of pregnancies^{1,2}. It is the most common medical complication of pregnancy whose incidence has continued to increase worldwide, and it is associated with significant maternal morbidity and mortality, accounting for about 50,000 deaths worldwide³.

Risk factors for preeclampsia include nulliparity, multifetal gestations, previous history of preeclampsia, obesity, diabetes mellitus, vascular and connective tissue disorders like systemic lupus erythematosus and antiphospholipid antibodies, age > 35 years at first pregnancy, smoking and African American race. Among primiparous women, there is a disparity among ethnic groups as the risk in African American women is twice that of Caucasian women⁴.

The connection between these risk factors and preeclampsia is poorly understood. The differences in risk among ethnic groups suggest a strong role for genetic factors in the pathogenesis of preeclampsia. Most theories on the etiology of preeclampsia suggest that the disease is a cascade triggered by combination of abnormal maternal inflammatory response, endothelial cell activation/damage with deranged hemodynamic milieu, and deranged immunity^{5,6}. The precise trigger that

unifies the deranged vascular, immune and inflammatory responses remains to be elucidated⁷. PE is considered a multisystem disorder, affecting several organs and maternal systems, including the vascular system, liver, kidney and brain. Despite the intensive research in this area, the etiology of PE remains unknown. PE seems to have a multifactorial cause and is also known as the "disease of theories". In fact, there are several hypotheses raised to explain its etiology. Some those theories propose modifications in the trophoblastic invasion, immunologic intolerance between maternal and fetal placental tissue, inflammatory changes in pregnancy and genetic modifications, underlying PE development⁷. Although its unknown cause, it is consensual that there are modifications occurring at different levels, like changes in placental perfusion, increased inflammatory response with changes in leukocyte activation, activation of the coagulation system, endothelial dysfunction and changes in lipid metabolism. The most accepted theory describes two stages for PE, stage 1 - reduced placental perfusion; stage 2 - multisystem maternal syndrome⁸. The complications of preeclampsia are include eclampsia, HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome, liver rupture, pulmonary edema, renal failure, disseminated intravascular coagulopathy (DIC), hypertensive emergency, hypertensive encephalopathy and cortical blindness⁹.

Myeloperoxidase (MPO) is a hemoprotein normally released from activated monocytes and neutrophils.



Traditionally viewed as a microbicidal enzyme, MPO also induces low-density lipoprotein oxidation, activates metalloproteinases, and oxidatively consumes endothelium-derived NO. The elevated plasma MPO level is a risk factor for myocardial events in patients with coronary artery disease¹⁰. Patients with preeclampsia display evidence of the inflammation and endothelial dysfunction associated with oxidative stress in the circulation, vasculature, and placenta. We hypothesized that MPO levels in the circulation and placental extracts from women with preeclampsia would be different from levels in women with normal pregnancies¹¹. Paraonase is associated in human serum with high density lipoprotein (HDL). Paraonase protects low density lipoprotein and HDL from oxidation. This protection is probably related to the ability of paraonase to hydrolyze some oxidized phospholipids¹² and/or cholesteryl linoleate hydroperoxides¹³. Serum paraonase activity was found to be reduced in a number of pathological conditions, including myocardial infarction, diabetes and hypercholesterolemia. Previous studies showed decreased serum paraonase activity in cases of preeclampsia^{14,15}.

METHOD

Two hundred and ten blood samples were collected from patients admitted to AL- Zahraa Teaching Hospital during the period from June 2013 to January 2014. Twenty seven patients were developed PE later on after follow up. Their ages range from 21-38 years. These patients were followed for up to five months (first reading at 16-20 week, second reading at 21-28 week and third reading at 29-40 week) for serial assessment for estimation of serum levels of MPO and PON-1 in the PE patients. Patients suffered from any other disease were not included in the current study. Control group consisted of one hundred and eighty subjects. They were pregnant women without preeclampsia and other complications. The control group samples were collected from AL- Zahraa Teaching Hospital in Annajaf City. These patients also were followed for up to five months (first reading at 16-20 week, second reading at 21-28 week and third reading at 29-40 week). Their ages range from 21-36 years. Blood samples were obtained from pregnant women with preeclampsia and Non-PE groups by vein puncture. Samples were allowed to clot at room temperature for 30 minutes, and then centrifuged at 3000 Xg for 20 minutes. Sera were removed and stored at -18 °C until analysis in disposable serum tubes.

RESULTS

The evaluation of the data indicated that the enrolled patients were distributed according to different trends. They were distributed according to the age, Parity, BMI and MAP. The characteristics of the enrolled preeclamptic patients are mentioned in Table (1, 2 and 3) by mean and the standard deviation (Mean \pm SD). There was significant ($p < 0.001$) elevation of the concentrations of MPO in preeclamptic patients when compared with those of the

non-preeclamptic group and there was significant ($p < 0.001$) decreasing the concentrations of PON in preeclamptic patients when compared with those of the non-preeclamptic group (Table 4) (A,B,C). 27 patients were followed up (the first reading from 16-20 week, the second reading from 21-28 week and the third reading from 29–40 week) for serial assessment of serum levels estimation of MPO and PON in preeclamptic patients (Table 4).

The linear regression analysis was used to examine the relationship of the levels of MPO and PON with ages of the preeclamptic and Non-preeclamptic group. No significant correlations were observed for the levels of MPO and PON with ages of the preeclamptic and Non-preeclamptic group.

The linear regression analysis was used to examine the relationship of the levels of MPO and PON with MAP of the preeclamptic and Non-preeclamptic group.

Significant positive correlations (Table 5 and Figure 1) were observed for the levels of MPO while significant negative correlations (Table 5 and Figure 2) were observed for the level of PON with MAP of the preeclamptic.

The linear regression analysis pointed out significant negative correlation between MPO with PON in preeclamptic patients (Figure 3)

Table 1: Characteristics of preeclamptic patients (16-20 week) included in the study.

Variable	Mean \pm SD	Range
Age (years)	28.93 \pm 5.45	21-38
Body mass index (kg/m ²)	24.26 \pm 2.61	20-29
Systolic pressure (mmHg)	116.44 \pm 6.57	97-124
Diastolic pressure (mmHg)	75.26 \pm 5.76	65-86
Mean arterial pressure (mmHg)	88.99 \pm 5.04	78.3-98
Parity	2.26 \pm 1.23	0-6

Table 2: Characteristics of preeclamptic patients (21-28 week) included in the study.

Variable	Mean \pm SD	Range
Age (years)	28.93 \pm 5.45	21-38
Body mass index (kg/m ²)	25.16 \pm 2.15	20-30.16
Systolic pressure (mmHg)	151.16 \pm 7.45	140-170
Diastolic pressure (mmHg)	97.56 \pm 6.33	90-114
Mean arterial pressure (mmHg)	108.05 \pm 4.11	106-118.6
Parity	2.26 \pm 1.23	0-6

Table 3: Characteristics of preeclamptic patients (21-40 week) included in the study.

Variable	Mean \pm SD	Range
Age (years)	28.93 \pm 5.45	21-38
Body mass index (kg/m ²)	27.31 \pm 2.06	22.2-33
Systolic pressure (mmHg)	152.24 \pm 6.07	145-172
Diastolic pressure (mmHg)	98.04 \pm 4.41	89-115
Mean arterial pressure (mmHg)	118.45 \pm 4.13	106.7-126.6
Parity	2.26 \pm 1.23	0-6



Table 4A: Serum MPO and PON levels in preeclamptic patients and the non-preeclamptic group (16-20 week).

Parameter	Subject	NO.	Mean ± SD	Range	P-value
MPO ng/ml	PE	27	26.79 ± 0.92	25.3-28.6	< 0.001
	NON-PE	180	14.71 ± 2.37	11.2-20.7	
PON mIU/ml	PE	27	156.41 ± 6.59	147-171	< 0.001
	NON-PE	180	187.67 ± 10.35	169-211	

Note: P-value < 0.001 mean significant

Table 4B: Serum MPO and PON levels in preeclamptic patients and the non-preeclamptic group (21-28 week).

Parameter	Subject	NO.	Mean ± SD	Range	P-value
MPO ng/ml	PE	27	31.39 ± 1.16	29.1 - 33.2	< 0.001
	NON-PE	180	14.81 ± 2.71	11.1 - 21.1	
PON mIU/ml	PE	27	145.44 ± 6.59	137 - 159	< 0.001
	NON-PE	180	184.77 ± 9.14	169 - 209	

Table 4C: Serum MPO and PON levels in preeclamptic patients and the non-preeclamptic group (29-40 week).

Parameter	Subject	NO.	Mean ± SD	Range	P-value
MPO ng/ml	PE	27	36.27 ± 0.76	34.5 - 37.8	< 0.001
	NON-PE	180	14.90 ± 2.22	10.9 - 19.7	
PON mIU/ml	PE	27	134.52 ± 6.57	124 - 146	< 0.001
	NON-PE	180	181.13 ± 9.97	163 - 204	

Table 5A: Serial assessment of serum levels of MPO and PON in 27 preeclamptic patients

Parameter	First Reading 16-20 week	Second Reading 21-28 week	Third Reading 29-40 week
MPO ng/ml	26.79 ± 0.92 A	31.39 ± 1.16 A*	36.27 ± 0.76 A*
PON mIU/ml	156.41 ± 6.59 D	145.44 ± 6.59 D*	134.52 ± 6.57 D*

Table 5B: Univariate analysis of MPO and PON with MAP of preeclamptic patients and Non-preeclamptic group.

Parameter	Preeclamptic		Non-Preeclamptic	
	r	P	r	P
MPO (ng/ml)	0.36	< 0.001	0.03	N.S
PON (mIU/ml)	0.34	< 0.005	0.07	N.S

DISCUSSION

When the results of MPO and PON-1 concentrations of patients were compared with the control group, the highest levels of the control group were 28.6 ng/ml and 171mIU/ml respectively, the lowest values of MPO and PON-1 concentrations in the group of patients were 25.3ng/ml and 147mIU/ml respectively. Thus it is clear that only the values of MPO of the patients and the control group did not overlap, in contrast PON-1 do not do so. These evidences suggest the use of measurements of MPO concentration as additional parameters in the management and prediction of PE. We can suggest a cut off value for MPO after more investigations. No Significant correlations were observed for the sera level of MPO and PON-1with ages of patients and the control group. These results are in agreement with Schwartz LB¹⁶ who found that there are no significant changes in serum MPO with respect to maternal age. The current results indicated that alterations of inflammatory markers in PE are independent on ages of patients. The reasons seem to be unclear and further investigations may be required to explain such reasons¹⁶. The linear regression analysis was used to examine the relationship of the levels of MPO and PON-1 with mean arterial pressure (MAP) of the patients and the control group. Significant positive correlations were observed for the level of MPO and PON-1 with the mean arterial pressure (MAP) of the patients, significant correlations could not be obtained in the group of healthy pregnant women. These results are in agreement with those reported by Shakow S.¹⁷ who found that in hypertensive pregnant women there is a release of placental factors that initiate a cascade of cellular and molecular events leading to endothelial and vascular smooth muscle cell dysfunction and thereby increased vascular resistance and arterial pressure. It was found a positive correlation between serum levels of MPO and diastolic and systolic blood pressure in PE. Endothelial dysfunction of PE has been associated with an exaggerated maternal inflammatory response to pregnancy. It has been hypothesized that placental hypoxia resulting from uteroplacental arterial insufficiency, amplifies the release of inflammatory stimuli into the maternal circulation¹⁸. Carreras L. showed that MPO can induce endothelial dysfunction and injury to ultra structure of placenta and umbilical vascular endothelium. This injury may play a role in the pathogenesis of pregnancy induced hypertension¹⁸.

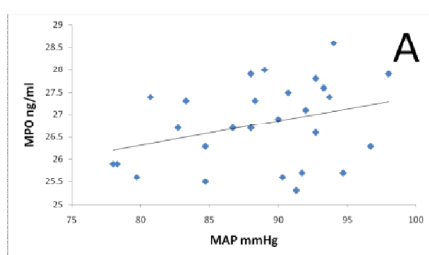


Figure 1: The correlation of MAP with MPO in: A) preeclamptic patients

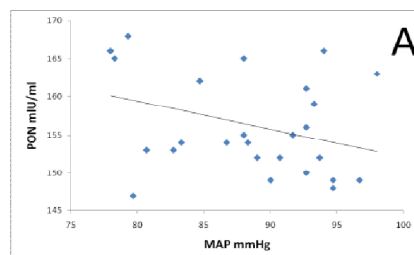


Figure 2: The correlation of MAP with PON in: A) preeclamptic patients

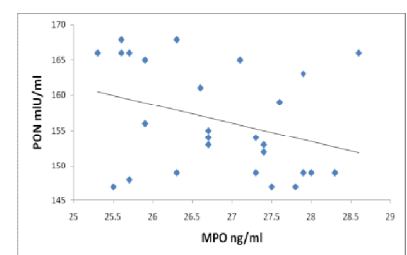


Figure 3: The correlation of MPO with PON in preeclamptic patients



Level of MPO in Preeclampsia

In the current study, MPO levels were significantly increased in women with preeclampsia. Serum MPO levels have been shown to increase with gestational age in the preeclamptic patients. This agreement with¹⁹ who showed MPO levels were significantly elevated in women with PE when compared with samples without preeclampsia. Serum MPO levels in patients with preeclampsia were contributed to the oxidative damage reported in the endothelium of women with preeclampsia. MPO can become sequestered in the sub-endothelial space through a process of endothelial transcytosis, resulting in the accumulation of MPO in the endothelial cell matrix. There it can be a potent source of reactive oxygen and nitrogen species. This disagreement with²⁰ who found no significant difference in baseline serum MPO levels between PE and Non-PE patients. Mast cells play a key role in allergic reactions and increase in numbers under inflammatory conditions. Extracellular tryptase, when present, may be a marker of mast cell activation in disease interestingly, increased MPO activity was observed in preeclamptic group. This observation could be explained to result of a study that reported by Cregar.²¹ These authors reported that MPO inhibits human mast cell tryptase in a time dependent manner. It is the native protein conformation of MPO and not its enzyme activity that is responsible for tryptase inhibition²¹. In the current study, MPO has negative correlation with PON and positive correlation with leukotrienes, this agreement with²².

Preeclampsia is proposed as a two-stage disorder: reduced placental perfusion usually results with an abnormal implantation and a maternal disorder characterized by endothelial dysfunction and subsequent pathophysiological changes. Reduced perfusion and abnormal implantation could be seen in IUGR or preterm labor without the maternal syndrome. This leads to the hypothesis that reduced placental perfusion must interact with maternal constitutional factors especially some immuno-genetic dysfunctions to generate the systemic pathophysiology of preeclampsia²³. Oxidative stress secondary to reduced placental perfusion leads to endothelial dysfunction. MPO is an oxidative enzyme and could link the two stages of preeclampsia. Pregnancy is associated with an inflammatory state, and inflammatory changes with neutrophil activation are exacerbated in preeclampsia (Holthe MR., 2005). Activated leukocytes, both monocytes and granulocytes which expressed MPO enzyme, generate excess reactive oxygen species resulting in oxidative stress²⁴. MPO is an oxidative enzyme that is abundantly expressed in the azurophilic granules of neutrophils and to a lesser extent in monocytes. MPO reacts with H₂O₂. MPO-H₂O₂ complex forms HOCl, OCl, and Cl₂. HOCl is the potent oxidant in the active neutrophils²⁵. The toxicity of H₂O₂ increases after it reacts with MPO. Another potentially important affect of MPO activity is consumption of nitric oxide and induction of endothelial dysfunction. MPO serves as a

catalytic sink for nitric oxide, impairs nitric oxide dependent vasodilation, and decreases nitric oxide bioavailability in cultured cells²⁶. Serum MPO levels serve as a strong and independent predictor of endothelial dysfunction in human subjects. They concluded that MPO-mediated endothelial dysfunction may be an important mechanistic link between oxidation-inflammation which have an important role of etiopathogenesis of preeclampsia and cardiovascular disease. Previously Bowen have reported that the serum concentration of MPO did not change in preeclampsia and eclampsia compared with normal pregnancy. Lastly, Gandley have demonstrated that MPO levels were significantly increased in the circulation of women with preeclampsia. Kim performed the study to determine whether genetic variability in oxidative stress-related enzymes contributes to individual preeclampsia susceptibility differences in the Korean population^{27,28}

Level of PON-1 in Preeclampsia

In the present study, results indicated that serum PON activity was lower significantly in preeclamptic group compared to non-preeclamptic. This is agreement with²⁹.

PON1 is antioxidant enzyme located in HDL that protect vascular tissue from oxidative damage by protecting low density lipoprotein and HDL from oxidation and responsible of the antioxidant activity of HDL. This protection is probably related to the ability of paraoxonase to hydrolyze some oxidized phospholipids and/or cholesteryl linoleate hydroperoxides. Serum PON activity was found to be reduced in a number of pathological conditions including myocardial infarction, diabetes and pregnancy complication including PE¹².

Ceruloplasmin oxidase was higher in normal pregnancies in comparison to other groups with pregnancy complications. These results of PON was thought to offer the cell protection from the damage caused by the increased oxidative stress associated with PE. Ceruloplasmin (ferroxidase activity), like PON known as oxidant defense enzyme and decreases significantly in pregnant women with complications¹⁷.

It has been suggested that an oxidant/antioxidant imbalance is associated with pregnancy failure. Increased oxidative stress may alter placental vasculature, the prostacyclin-thromboxane balance and culminating in PE. The decrease in PON1 activity may play an important role in pathogenesis of early PE detection through increased susceptibility to lipid peroxidation³⁰. Muge³¹ concluded that patient with complete hydatidiform mole are exposed to oxidative stress, which may have a role in the pathogenesis of the disease. Serum paraoxonase and arylestrase activities decrease in preeclampsia, and this situation may be associated with increased LOOH in these patients. Lower PON activity investigated also in normal pregnancy by Emre³² and in pregnancy failure by Harun.³⁰

PON1 has antiatherogenic and anti-inflammatory properties, resulting from its ability to destroy modified



phospholipids and to prevent accumulation of oxidized lipids in lipoproteins. LDL particles can be protected from free radical-induced oxidation by an HDL-linked enzyme PON1. Arylesterase (AE), one of the enzymatic activities of PON1, is known to play a protective role against peroxidation of LDL and other lipoproteins³³.

The decrease serum PON1 activity in PE patients may contribute to insulin resistance and atherosclerotic heart disease and/or the inactivation of the enzyme itself due to oxidative stress, hyperandrogenism, nonenzymatic glycation. Moreover, the impairment of PON1 activity may be the result of structural modification of Apo A-I, because Apo A-I is necessary to stabilize the structure of PON1 and maintain PON1 activity.

However, under conditions of oxidative stress PON1 can be oxidized or undergoes nitration, when exposed to peroxynitrite (ONOO⁻) which leads to structural and functional modification of Apo A-1³⁴.

The serum PON1 activity is affected by oxidative stress. PON1 activity is inhibited by reactive oxygen species and also, the serum PON1 expression is down-regulated by oxidative stress and this can explain the negative correlation between PON1 and MPO in PE³⁴.

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