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Inflammatory Markers in Pre-eclampsia

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Abstract

Pre-eclampsia, a hypertensive disorder that affects some pregnants, is considered as a major cause of maternal and fetal death. Inflammation and oxidative stress may contribute to the pathophysiology of pre-eclampsia.The aim of this study is to evaluate the values of oxidative stress parameters and inflammatory markers in blood of normal and pre-eclamptic pregnants. Serum levels of malondialdehyde, peroxynitrite, C-reactive protein, and tumour necrosis factor alpha, besides urinary protein, had been determined in 25 pre-eclamptic and 25 normotensive pregnant women. The results of this research show that in the pre-eclampsia group; serum malondialdehyde, peroxynitrite, C-reactive protein, and tumour necrosis factor alpha levels were significantly higher than in the normotensive group. Serum malondialdehyde showed significant positive correlation with C-reactive protein and tumour necrosis factor alpha. In conclusion: The inflammatory markers; C-reactive protein and tumour necrosis factor alpha and oxidative stress markers; malondialdehyde and peroxynitrite are all increased in pre-eclampsia. These data revealed the role of inflammation and oxidative stress factors in pre-eclampsia.

***Keywords*:** pre-eclampsia, oxidative stress markers, inflammatory markers, tumour necrosis factor alpha

1. Introduction

Pre-eclampsia (PE) is one of the serious complications which may happen throughout pregnancy [1], hypertension and proteinuria are the main characters and usually begins in the second trimester of gestation. Its incidence is about 2-10% of all pregnancies worldwide [2]. Despite wide studies, the aetiology and pathogenesis of PE are not definitely known, and the absolute cause for this disorder is uncertain [3]. It has been suggested that changes in lipid profile and leukocyte stimulation enhanced the oxidative stress and inflammatory reaction in maternal blood [4] [5] [6] [7]. In PE the impaired blood flow to placenta is a likely cause of developing oxidative stress that leads to damage in the placenta causing inflammation and liberation of proinflammatory cytokines and acute phase proteins [8] [9]. Tumour necrosis factor alpha (TNF-alpha) is a proinflammatory cytokine that seems to have an important effect in immune activation in PE [10]. C-reactive protein (CRP) that is produced by the liver is one of the acute phase proteins which elevates rapidly in response to inflammatory processes [11]. Recent researches show the role of oxidative stress (which is an imbalance between antioxidant defense and free radical formation) in PE as it associated with lipid modification and the increase in the placental and systemic lipid peroxidation, proposed that oxidative stress may lead to dysfunction of endothelial cells. One of the oxidative stress markers is malondialdehyde (MDA) which is considered as the end product of lipid peroxidation [12], so MDA values may reveal the oxidative disturbance in PE [13]. Peroxynitrite, a strong oxidant, is produced from the reaction between nitric oxide and superoxide anions under oxidative state. Nitric oxide is a free radical which is produced by endothelial cells, it can lead to cellular damage. Recent evidence showed that most of its damaging effect is due to peroxynitrite formation [14].

1.1. Aim of the study:

Our study aims are estimation and comparison of the oxidative stress parameters and inflammatory markers between normal and pre-eclamptic pregnancies, and to find out if there is any relationship between MDA and each of CRP and TNF-alpha in PE.

2. Subjects and Methods:

This study represents a case-control study, it was operated in al-Batool teaching hospitals, involving

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50 pregnant women in the third trimester of gestation, their ages ranged between (20-30) years, they were classified into two groups; the first one is the control group; included 25 apparently healthy pregnant women, and they are within the following criteria: primigravida or multiparas, pregnant with a singleton pregnancy, having gestational ages between 24-39 weeks according to the date of last menstrual cycle, clinical examination and ultrasound findings. We exclude the following criteria; Multiple pregnancy, history of chronic hypertension, diabetes mellitus, thyroid disorders, blood disease, hepatic disease, urinary tract infection and vaginal or cervical inflammation. The second group is the patient group; consisted of 25 pre-eclamptic pregnant women with the same previous inclusion and exclusion criteria. They were diagnosed to have pre-eclampsia according to the diagnostic criteria of this disorder [1] and they were on treatment with antihypertensive drugs at time of sampling. Before data collection we informed all participants about the objectives and the protocol of the study.

A sample of 5mL venous blood was obtained from each women, after overnight fasting, for measurement of; serum CRP concentration using slide agglutination, CRP latex test kit (semi-quantitative method) [15], TNF-alpha by ELISA [16] the oxidant status was studied by estimating serum MDA levels determined by colorimetric method [17], serum peroxynitrite levels by the modulated method of Vanuffelen *et al*. [18]. For detection of urinary protein, 3-5ml were collected from random voided urine for qualitative determination of proteinuria by reagent strips [19]. Anthropometric measurements including physical examination of body, weight in kilogram and height in centimeters. Body mass index (BMI) was calculated using the formula: BMI= weight / (height)^2, as indicated by the World Health Organization (WHO) [20].

2.1. Statistical Analysis

The SPSS statistical program 17.0 was used to analyze the data which were expressed as (mean±standard deviation) for variables. Student's t-test was done to compare variables of the studied groups. Pearson's correlation test was performed to determine the relationship between the MDA and each of CRP and TNF-alpha.

3. Results

Table 1 shows that blood pressure values (systolic and diastolic) and BMI were higher in the patient group. Table 2 showed that serum levels of CRP, TNF-alpha, MDA and peroxynitrite were significantly higher in the patients. Using Person's correlation test, the MDA showed a significant positive correlation with TNF-alpha ($r=0.779$, $p<0.0001$),(figure 1) . Figure 2 revealed that MDA and CRP levels were positively correlated (using Person's correlation test: $r=0.488$, $p=0.013$).

Table (1):- Descriptive statistics among the studied groups.

parameters	Patients: N=25		Controls: N=25		P* value
	mean	Standard deviation	mean	Standard deviation	
CRP (mg/L)	21.12	13.09	9.840	5.161	0.0001
TNF-alpha (pg/ml)	71.36	34.991	26.72	32.535	0.0001
MDA (µmol/L)	4.35	1.184	2.048	1.0528	0.0001
Peroxynitrite (µmol/L)	85.95	7.892	75.912	11.362	0.01

*Student t-test

Table (2):- Comparison of the studied parameters between the controls (normotensive), and the patients (pre-eclamptic) pregnant women.

Parameters	Patients: n=25		Controls: n=25		*P value
	Mean	Std. Deviation	Mean	Std. Deviation	
diastolic B.P (mm Hg)	96.8	9.987	70.0	8.165	0.0001
systolic B.P (mm Hg)	149.8	10.75	113.0	11.726	0.0001
gestational age (weeks)	34.48	3.917	35.24	4.146	0.508
BMI (kg/m^2)	30.4	2.164	27.66	1.721	0.0001

*Student t-test

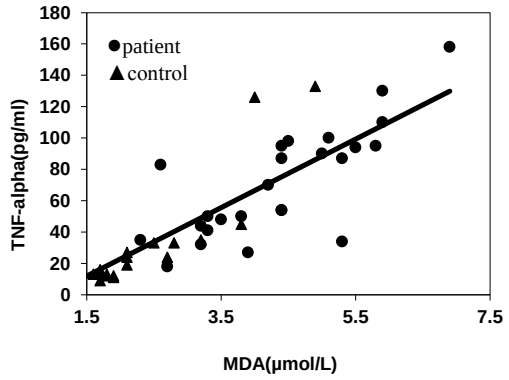

Fig. (1) Relationship between MDA and TNF-alpha

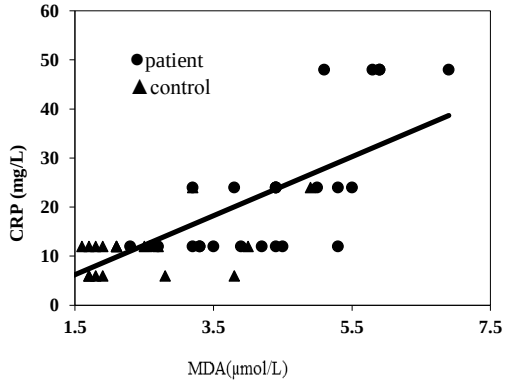

Fig. (2) Relationship between MDA and CRP

4. Discussion

Pre-eclampsia is a complex disorder affecting multisystem in pregnant women, it is characterized by hypertension and proteinuria [21].

In this study as we expected, blood pressure values were higher in the patient group and the same for the BMI values were higher in this group.

Our study revealed that serum CRP concentrations were markedly higher in patients which supports the presence of inflammatory response in PE and this were accepted with the results of other researcher [22] [23]. This was also in accordance with the study results of DanMihu *et al*. [24], who found a higher concentration of CRP in PE.

Significant higher levels of TNF-alpha were seen in the patient group (71.36 pg/ml) compared to the control group (26.72 pg/ml); (p=0.0001). This is in line with results of Bayrama *et al.* and Sharma *et al.* [25][26] that found higher concentrations of TNF-alpha levels in pregnant women with PE. This results power the possibility that systemic inflammation is contributed to the pathogenesis of PE [27].

Our results also indicated high levels of serum MDA in patients, which is consistent with the study of Johnkennedy *et al*. [28] who showed higher MDA levels in pre-eclamptic compared to normotensive women. Moreover, this finding was similar to results obtained by Jammalamadaga *et al.* [29] who found significant elevation in serum MDA levels in PE compared to normal pregnant women.

Our results detected a significant increase of peroxynitrite values in the patient group. This may be due to overproduction of the nitric oxide in PE and under conditions of oxidative stress, it reacts with superoxide anions leading to production of peroxynitrite that can affect vascular function. This is in agreement with results of other researchers. [30]

In our study we assessed the correlation between MDA and each of TNF-alpha and CRP, we found that MDA correlated positively with TNF-alpha (P=0.0001) and CRP (P=0.013), this result comes in coinciding with the studies of Babu *et al.* [31] and Bharadwaj *et al.* [32].

Finally, our findings confirm that inflammatory reactions and oxidative stress are associated with PE, furthermore, the observed results revealed a relationship between oxidative stress and inflammatory response in PE.

Conflicts of interest:

There are no conflicts to declare

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