Oxidative Stress and Dyslipidemia as Indicators of Pathogenesis of Preeclampsia in Pregnant Sudanese Women

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Abstract

Background: Preeclampsia (PE) still ranks as one of obstetrics major problems and is still a serious threat, mainly in underdeveloped countries where its incidence and mortality rates are higher and is a major cause of preterm birth and intra-uterine growth restriction. **Aim:** To evaluate the role of oxidative stress and dyslipidemia as indicators of pathogenesis and risks of preeclampsia in pregnant Sudanese women attending Wad-Medani Obstetrics and Gynecology Teaching Hospital. **Material and Method:** This was a cross-sectional (case-control) study carried out in preeclamptic pregnant Sudanese women attending Wad-Medani Obstetrics and Gynecology Teaching Hospital. A total of 208 pregnant women were enrolled in the study, 111 patients and 97 women with normal pregnancy as controls; pregnant women suffering from any systemic or endocrine disorder were excluded. We compared the serum levels of total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, nitric oxide, and total antioxidant capacity between preeclamptic and controls. **Result and Conclusion:** Pregnant women with increase in BMI have a higher chance of developing PE. Low level of high-density lipoprotein cholesterol and high level of low-density lipoprotein cholesterol define that dyslipidemia increases the risk of PE. Decreased levels of NO and TAC might reflect the oxidative stress and likely contribute to the pathophysiological mechanisms of PE.

Keywords

1. Introduction

Pregnancy is one of the most important periods in the life of a woman, a family

and a society [1]. The success of pregnancy is a result of ongoing interactions between the placenta and the maternal immune and cardiovascular systems [2].

Pregnancy is a transient condition, but when it is complicated by preeclampsia (PE), it has lasting effects on both the mother and the fetus [3].

PE is a pregnancy multisystem disorder characterized by hypertension (≥140/90 mmHg), proteinuria (≥300 mg/24 hrsor ≥ 1 + dipstick) with or without edema, that appear after 20 weeks of gestation in a previously normotensive non-proteinuric pregnant women [4].

PE found uniquely in the pregnant patient and one that has puzzled scientists for years and one of the "great obstetrical syndromes" [5], is characterized by systemic inflammation, endothelial cell dysfunction, excessive thrombin generation, an anti-angiogenic state and is often associated with multiple organ involvement [6]. However, PE is fundamentally a placental disease which manifests itself, in most cases, by involvement of the vascular (*i.e.* hypertension) and renal systems (*i.e.* proteinuria) [7].

During healthy pregnancy, there is an elevation in oxygendemand along with an increase in the production of reactive oxygen species (ROS) to carry out signaling for physiological processes in pregnancy, such as oocyte maturation, ovarian steroidogenesis, ovulation, implantation, blastocyst formation, luteolysis and luteal maintenance [8]. Preeclamptic women can present associated endothelial dysfunction, dyslipidemia and aggravated systemic production of free radicals [9].

PE is one of the most common complications of human pregnancy with an overall incidence 2% - 12% [10] and the syndrome results in more than 63,000 maternal deaths worldwide annually, among which 75% are experienced in a mild form, and 25% in a severe form [11]. Prevalence of preeclampsia has increased by up to 30% over the last decade [12].

The exact cause of PE remains uncertain. Therefore, PE is still a disease of theories [13]. Although the cause remains largely unknown, the pathogenesis is thought to occur in two main phases. The first stage is asymptomatic, characterized by abnormal placental development during the first trimester resulting in placental insufficiency and the release of excessive amounts of placental materials into the maternal circulation. This in turn leads to the second, symptomatic stage, where in the pregnant woman develops characteristic hypertension, renal impairment, and proteinuria and is at risk for the hemolysis, elevated liver enzymes and low platelet account (HELLP) syndrome, eclampsia, and other end organ damage [14]. At the cellular level, preeclampsia is associated with the release of free radicals by the placenta and therefore generation of oxidative stress. Placenta-borne oxidative and stresses are even sometimes considered as the major molecular determinants of the maternal disease [15].

As PE is considered as a leading cause of maternal mortality and morbidity, measurement of some biochemical markers can enhance the screening and prediction of PE, and therefore the early detection and intervention can limit its progression and harmful effects.

Research works on the PE and particularly the indicators of pathogenesis are lacking in Sudan. Consequently, this study was conducted to clarify some indicators of pathogenesis of PE in Sudanese preeclamptic women.

Objectives of this study are to estimate the serum lipid profile (TC, TG, LDL, HDL) for evaluating the dyslipidemia in preeclamptic women and to test the association of serum nitric oxide (NO) and total antioxidant capacity (TAC) with the development of preeclampsia.

2. Material and Methods

This was a cross-sectional (case-control) study conducted to evaluate the role of oxidative stress and dyslipidemia as indicators of pathogenesis of preeclampsia in pregnant Sudanese women attending Wad-Medani Obstetrics and Gynecology Teaching Hospital from January 2015 to January 2016.

A total of two hundred and eight pregnant women were included in this study. They were selected from the Wards of the Hospital at admission before starting treatment. Informed consent was obtained from each participant before been recruited in to the study. The pregnant women were two groups; patients group of 111 preeclamptic pregnant women, and control group of 97normal pregnant women.

2.1. Inclusion Criteria

Preeclamptic women with blood pressure ≥ 140/90 mmHg, and proteinuria ≥300 mg/24 hrs or ≥1 + dipstick) were included. The controls were healthy pregnant women with no past history or family history of PE.

2.2. Exclusion Criteria

For both patients and controls: pregnant women with pre-gestational cardiac, hepatic or renal disorders, diabetes mellitus, primary or secondary lipid disorders, severe anemia, those who suffer from any other systemic or endocrine disorder were excluded.

A questionnaire was designed to obtain personal data, anthropometric measurements, social and medical information, and clinical investigations.

5 ml of blood from the median cubital vein was drawn from each participant and putinplain containers, left at room temperature for 30 minutes to clot and then centrifuged for 20 minutes at 5000 rpm. Then serum was separated and used for the measurement of TC, LDL, HDL, TG, NO and TAC.

Levels of TC, LDL, HDL, TG were measured using fully automated A15 chemical analyzer manufactured by Biosystems Company S.A Costa Brava 30, 08030 Barcelona (Spain).

The serum NO and total TAC were measured by Huma Reader HS Microtiter plate ELISA Reader manufactured by Bio Assay Systems Company. Corporate Place, Hayward, CA 94545, USA. Website: http://www.biosystems.com/.

Data were statistically analyzed by Statistical Package for the Social Sciences

(SPSS) software, version 20. The analysis was done by independent student t-test, chi-square test, Pearson's correlation, multiple linear regression. *P*-value ≤ 0.05 was considered to be statistically significant.

3. Results

The body mass index of preeclamptic women was significantly higher than that of normal pregnant women (25.33 ± 0.16 versus 24.65 ± 0.18, *p* = 0.005) (Figure 1). The systolic blood pressure/diastolic blood pressure of the preeclamptic women showed significant elevation compared to normal pregnant women (148.83 ± 0.89/96.85 ± 0.44 versus 108.04 ± 0.78/74.90 ± 0.57, *p*-values were < 0.001 and <0.001 respectively) (Figure 2).

Table 1 shows the characteristics of preeclamptic patients and controls regarding residence area and parity. *Note*: The majority of preeclamptic women have family history of PE (82.9%), no history of previous PE (71.2%) and late onset of PE (97.3%).

The biochemical parameters of cases and controls were presented as mean ± SEM. All the measured parameters were differed significantly between the two study groups (Table 2). The TC, LDL and TG were significantly higher in preeclamptic women than controls (*p*-values were 0.001, <0.001 and 0.007 respectively). The HDL level was significantly decreased in preeclamptic patients when compared with control group (*p* < 0.001). Levels of NO and TAC were significantly lower (*p*-values ≤ 0.001) in preeclamptic women than control group.

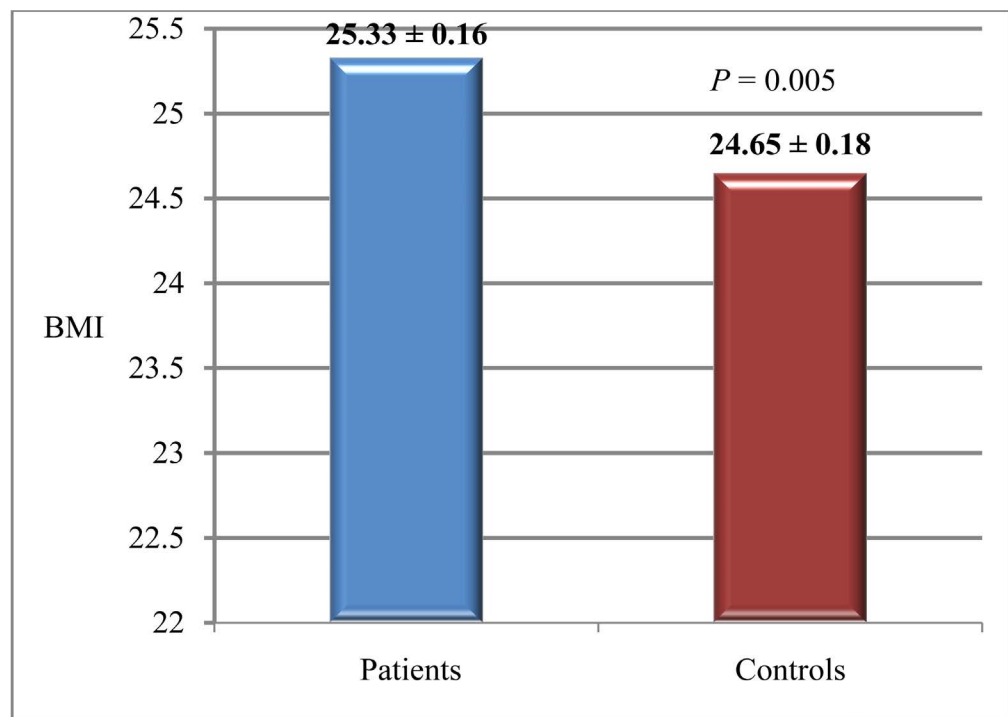Pregnant women that have high level of TC, LDL, and low level of HDL were

Figure 1. The mean of body mass index of the preeclamptic patients and controls.
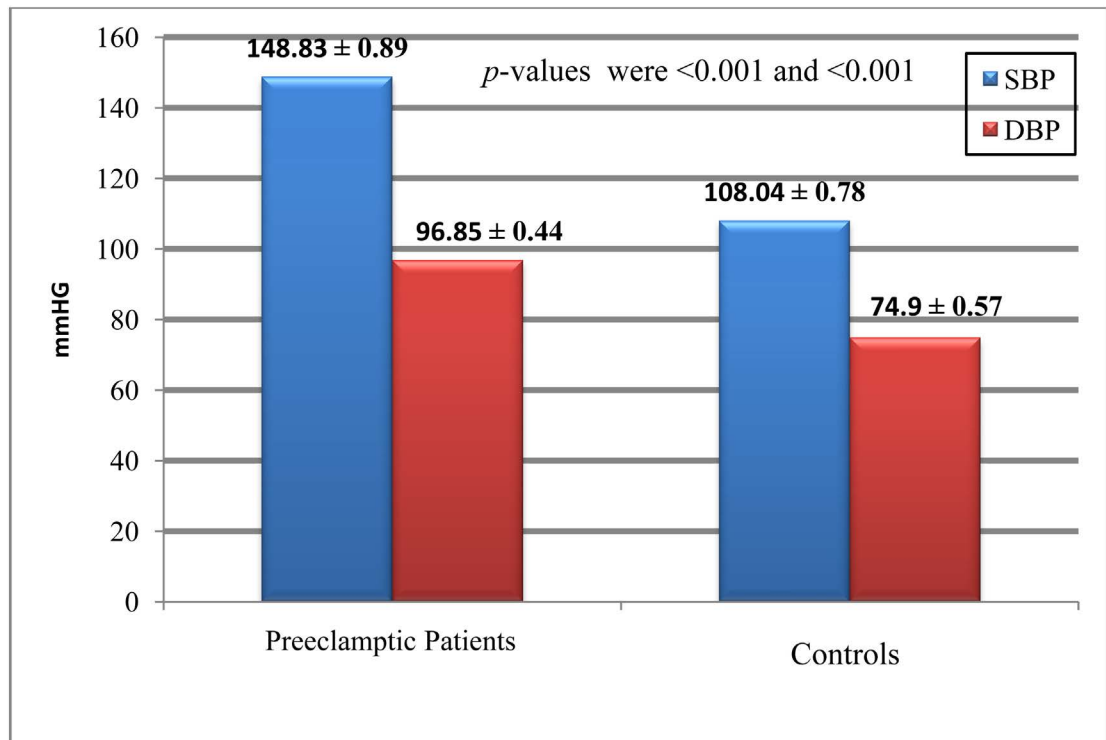
Figure 2. The systolic blood pressure (SBP) and diastolic blood pressure (DBP) of preeclamptic patients and controls.

Table 1. Characteristics and description of study groups.

Characteristic	Patients	Controls	Total	p-value
Age				
	27.09 ± 0.62	27.30 ± 0.62	208 (100%)	0.811
Gestational age				
	38.16 ± 0.12	38.76 ± 0.15	208 (100%)	0.002
Residence Area				
Rural	64 (57.7%)	57 (58.8%)	121 (58.2%)	
Urban	47 (42.3%)	40 (41.2%)	87 (41.8%)	0.889
Total	111 (100%)	97 (100%)	208 (100%)	
Parity				
Primiparous	54 (48.6%)	37 (38.1%)	91 (43.8%)	
Multiparous	41 (36.9%)	48 (49.5%)	89 (42.8%)	
Grand multiparous	16 (14.4%)	12 (12.4%)	28 (13.5%)	0.185
Total	111 (100%)	97 (100%)	208 (100%)	

more likely to develop PE compared with pregnant women with normal levels. Preeclamptic women tended to develop oxidative stress by 7.6 times for NO and 2.6 fold for TAC which in turn leads to development of PE (**Table 3**).

3.1. Correlation of Measured Parameters with NO

Table 4 shows the correlation of BMI, blood pressure, TC, LDL, HDL, TG and

Table 2. Comparison of biochemical parameters of the study groups.

Parameter	Patients (N = 111)	Controls (N = 97)	p-value
TC	155.34 ± 3.64	137.61 ± 3.68	0.001
LDL	101.76 ± 2.43	76.68 ± 2.29	<0.001
HDL	36.91 ± 0.52	43.22 ± 0.97	<0.001
TG	142.26 ± 2.68	129.96 ± 3.66	0.007
NO	61.69 ± 1.34	79.33 ± 1.06	<0.001
TAC	230.68 ± 10.68	291.66 ± 8.30	<0.001

Table 3. Comparison of risk estimate considering the parameters of lipid profile, tissue damage and oxidative stress between preeclamptic women and controls.

Parameter	Patients	Controls	Total	p-value	Chi value	OR (CI: 95%)
TC						
Normal	95 (85.6%)	87 (94.6%)	182 (89.7%)			
High	16 (14.4%)	5 (5.4%)	21 (10.3%)	0.111	3.243	2.414 (0.904 - 6.449)
Total	111 (100%)	92 (100%)	203 (100%)			
LDL						
Normal	103 (92.8%)	95 (99%)	198 (95.6%)			
High	8 (7.2%)	1 (1.0%)	9 (4.4%)	0.039	4.705	7.379 (0.906 - 60.103)
Total	111 (100%)	96 (100%)	207 (100%)			
HDL						
Low risk	73 (65.8%)	85 (89.5%)	158 (76.5%)			
High risk	38 (34.2%)	10 (10.5%)	48 (23.3%)	<0.001	15.066	4.070 (1.942 - 8.530)
Total	111 (100%)	95 (100%)	206 (100%)			
TG						
Normal	108 (97.3%)	84 (97.9%)	202 (97.6%)			
High	3 (2.7%)	2 (2.1%)	4 (2.4%)	0.884	0.062	1.076 (0.607 - 1.906)
Total	111 (100%)	96 (100%)	206 (100%)			
NO						
Low risk	33 (29.7%)	74 (76.3%)	107 (51.4%)			
High risk	78 (70.3%)	23 (23.7%)	101 (48.6%)	<0.001	44.922	7.605 (4.090 - 14.139)
Total	111 (100%)	97 (100%)	208 (100%)			
TAC						
Low risk	13 (11.7%)	25 (25.8%)	38 (18.3%)			
High risk	98 (88.3%)	72 (74.2%)	170 (81.7%)	0.011	6.855	2.618 (1.254 - 5.464)
Total	111 (100%)	97 (100%)	208 (100%)			

Table 4. Correlation of measured parameters with NO.

Parameter	Correlation coefficient (r)	p-value
BMI	−0.075	0.285
Systolic blood pressure	−0.493**	<0.001
Diastolic blood pressure	−0.538**	<0.001

Continued

TC	−0.174*	0.013
LDL	−0.270**	<0.001
HDL	0.180**	0.009
Triglyceride	−0.133	0.055
TAC	0.181**	0.009

Correlation is significant at 0.01 level; correlation is significant at 0.05 level, r: 0.1 - 0.3 weak correlation, 0.4 - 0.6 moderate correlation, 0.7 - 0.9 strong correlation.

TAC with NO. NO was negatively correlated with SBP (r = −0.493, $p \leq 0.001$), DBP (r = −0.538, $p \leq 0.00$), TC (r = −0.174, $p = 0.013$), LDL (r = −0.270, $p \leq 0.001$), TG (r = −0.133, $p = 0.055$), BMI (r = −0.075, $p = 0.285$), while it was positively correlated with HDL (r = 0.180, $p = 0.009$) and TAC (r = 0.181, $p = 0.009$) Correlation of measured parameters with TAC.

Correlation of BMI, blood pressure, TC, LDL, HDL, LDH and NO with TAC is shown in Table 5. TAC was negatively correlated with SBP (r = −0.285, p = <0.001), DBP (r = −0.268, $p \leq 0.001$), BMI (r = −0.063, $p = 0.365$), TC (r = −0.006, $p = 0.937$), LDL (r = −0.086, $p = 0.219$), while it was positively correlated with HDL (r = 0.227, $p = 0.001$) and NO (r = 0.181, $p = 0.009$).

3.2. Multiple Linear Regression Analysis of the PE-Associated Risk and Complication Factors

Multiple linear regression analysis with forward elimination was conducted to determine among the significant PE-associated risk factors what were the most significant factors that actually contribute to the development of PE as indicated by SBP and DBP.

Because the hypertension is the main clinical manifestation of PE, SBP and DBP were taken as dependent variable with PE-associated risk factors (BMI, lipid profile, TAC and NO) as independent variables of risk estimate. SBP and DBP were taken in two different models.

3.2.1. Systolic Blood Pressure Model

From the output of the multiple linear regression for PE-associated risk factors, the most significant factors that predict the development of PE were BMI (p = 0.036, β = 0.112), LDL ($p \leq 0.001$, β = 0.277), HDL ($p \leq 0.001$, β is −0.328), TAC ($p = 0.028$, $\beta = −0.121$) and NO ($p \leq 0.001$, $\beta = −0.318$) as shown in Table 6. These results indicate that for an increase of one unit in standard deviations of BMI and LDL the expected increase in standard deviation of SBP was 0.112 and 0.277 respectively. A decrease of one unit in standard deviations of HDL, TAC and NO the expected increase in standard deviation of SBP was 0.328, 0.121 and 0.318 respectively.

The regression lines between SBP and BMI, LDL, HDL, NO, TAC and CK are shown in Figure 3. Although TC and TG were significant PE-associated risk factors, they were eliminated from the multiple linear regression analysis model.

Table 5. Correlation of measured parameters with TAC.

Parameter	Correlation coefficient (r)	p-value
BMI	−0.063	0.365
Systolic blood pressure	−0.285**	<0.001
Diastolic blood pressure	−0.268**	<0.001
TC	−0.006	0.937
LDL	−0.086	0.219
HDL	0.227**	0.001
NO	0.181**	0.009

Correlation is significant at 0.01 level; correlation is significant at 0.05 level, r: 0.1 - 0.3 weak correlation, 0.4 - 0.6 moderate correlation, 0.7 - 0.9 strong correlation.

Table 6. Multiple linear regression analysis of the biochemical parameters associated with the risks of PE.

Dependent variable	Parameter	Un standardized coefficient		Standardized coefficient	t	P-value
		B	SE	β		
	BMI	1.405	0.666	0.112	2.111	0.036
	LDL	0.233	0.046	0.277	5.038	<0.001
SBP	HDL	−0.900	0.154	−0.328	−5.845	<0.001
	TAC	−0.026	0.012	−0.121	−2.213	0.028
	NO	−0.454	0.081	−0.318	−5.619	<0.001
	BMI	0.937	0.362	0.136	2.585	0.010
	LDL	0.145	0.025	0.313	5.762	<0.001
DBP	HDL	−0.342	0.084	−0.226	−4.082	<0.001
	TAC	−0.013	0.006	−0.110	−2.022	0.045
	NO	−0.297	0.044	−0.377	−6.743	<0.001

B: (slope of regression line) the size of the average difference in the dependent variable that corresponds with a one-unit difference in the independent variable, β: the rate of change in dependent variable per unit change in independent variable).

3.2.2. Diastolic Blood Pressure Model

From the output of the multiple linear regression for PE-associated risk factors, the most significant predictors for development of PE were BMI ($p = 0.010$, $\beta = 0.136$), LDL ($p \leq 0.001$, $\beta = 0.313$), HDL ($p \leq 0.001$, $\beta = −0.226$), TAC ($p = 0.028$, $\beta = −0.110$) and NO ($p \leq 0.001$, $\beta = −0.377$) as presented in Table 6. These results indicate that for an increase of one unit in standard deviations of BMI and LDL the expected increase in standard deviation of SBP was 0.136 and 0.313 respectively. For a decrease of one unit in standard deviations of HDL, TAC and NO, the expected increase in standard deviation of SBP was 0.226, 0.110 and 0.377 respectively.

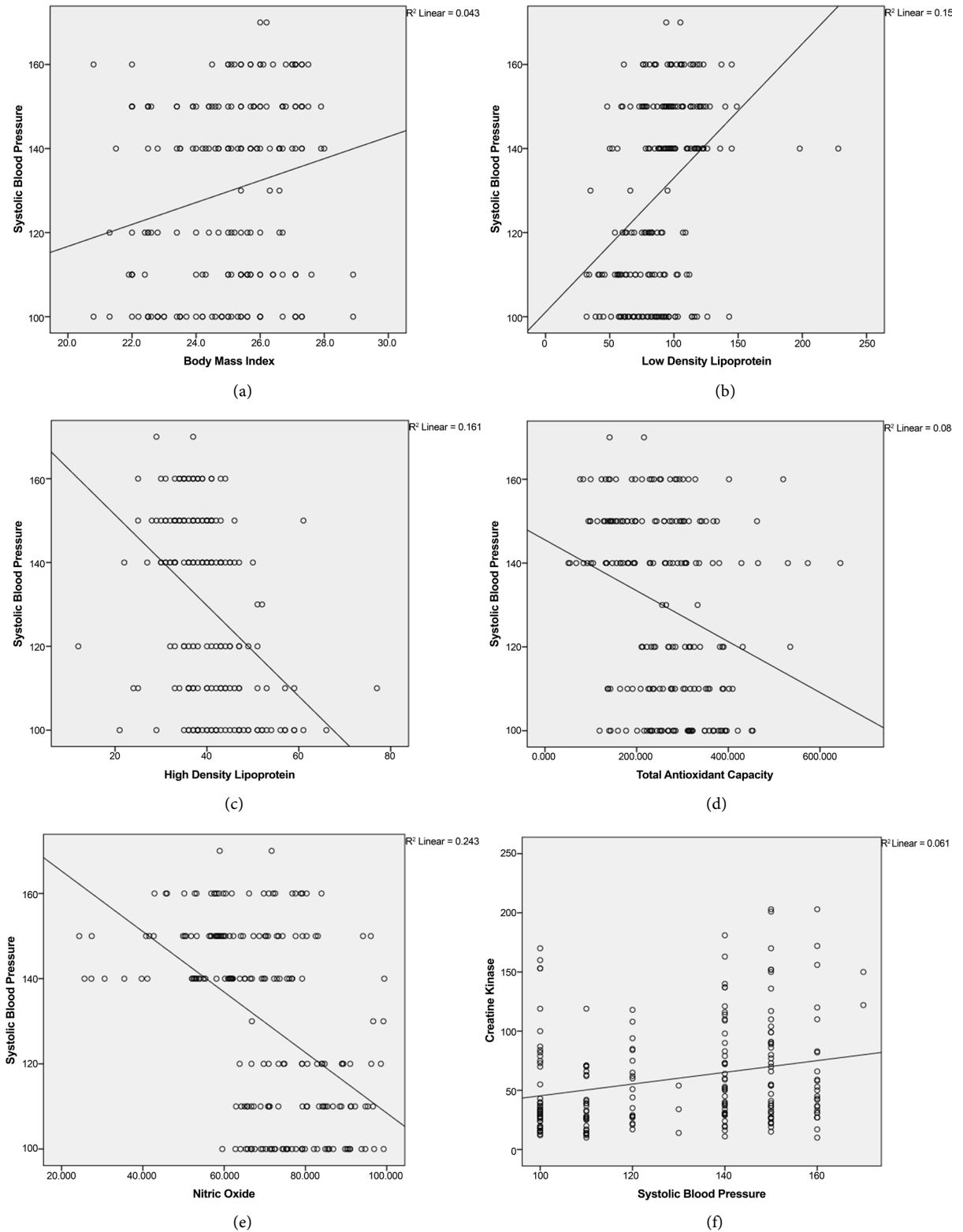The linear relationship between DBP and BMI, LDL, HDL, NO, TAC are shown in Figure 4.

Figure 3. Linear relationship between SBP and biochemical parameters.

4. Discussion

Preeclampsia is a multisystem disorder that remains a major cause of maternal
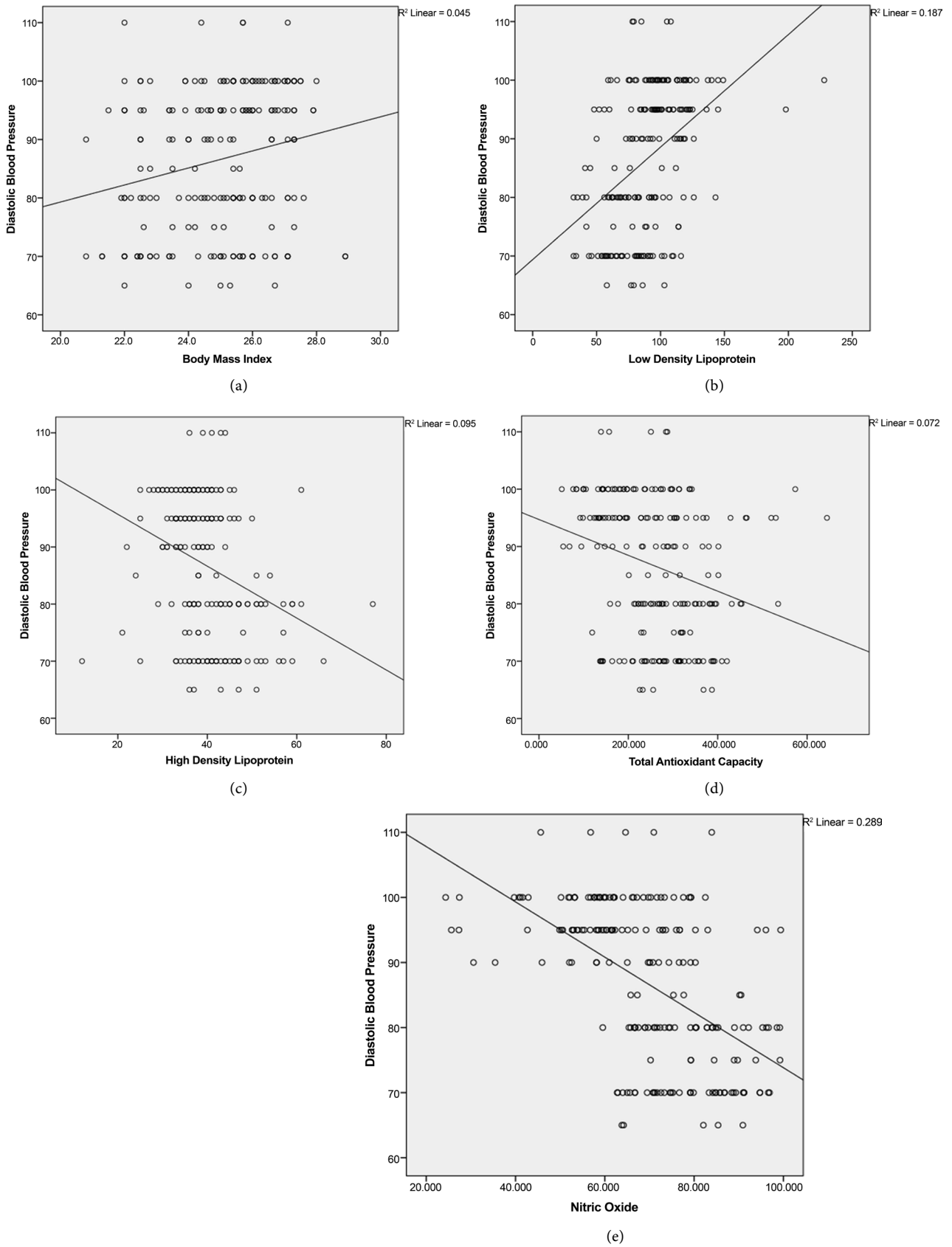
Figure 4. Linear relationship between DBP and biochemical parameters.

and fetal morbidity and mortality. Yet, no preventive measures are known to preclude the occurrence of the disease. Free radical damage and several metabolic derangement have been implicated in the pathophysiology of this condition [16]. This study aimed to evaluate the role of oxidative stress, dyslipidemia and markers of tissue damage as indicators of pathogenesis and risk of preeclampsia in pregnant Sudanese women.

In the present study, the ages of the two study groups were not statistically different, while the body mass index was significantly higher in preeclamptic women than control group.

Pregnancy is associated with physiologic hyperlipidemia, and in normal pregnancy this feature is not atherogenic, and attributed to hormonal changes [17]. Pregnancy-related disorders such as PE are associated with a dysregulation of lipid metabolism manifesting in adverse maternal blood lipid levels [18] [19]; in consistency, the present study showed marked increased levels of TC, TG and LDL in preeclamptic women than controls, while preeclamptic women revealed significant decrease in HDL level as compared to controls.

These findings agree with other studies. It was reported that there was a significant increase in TC, LDL and TG with significant decrease in HDL in preeclamptic group compared to normotensive group and stated that dyslipidemia plays an important role in the pathogenesis of PE [20]-[25].

The mechanisms underlying dyslipidemia in PE are implicit. One possibility; inconsequential gestational insulin resistance in PE probably increases the mobilization of fatty acid from visceral adipocytes, leading to over production of VLDL by the liver, and suppresses the activity of lipoprotein lipase, culminating in elevated serum TG concentration and reduced serum HDL level which is major risk factor for vascular dysfunction in PE [26]. Alternatively, PE is a state of hypoestrogenemia, which leads to decreased expression of VLDL/apo E receptors resulting in reduced transport of VLDL to fetal compartment and therefore occurrence of maternal hypertriglyceridemia [3] [27]. Further LDL taken up by the fetus is decreased due to reduced fetoplacental perfusion leading to increased LDL [28]. The elevated TG result in increased atherogenic small dense LDL and reduced HDL levels [29]. For the dyslipidemia and PE association, two mechanismsare suggested: firstly, dyslipidemia may induce endothelial dysfunction secondary to oxidative stress and hence occurrence of PE [30]. Secondly, dyslipidemia may impair trophoblast invasion by the deposition in predisposed vessels, such as the uterine spiral arteries and contributes to the endothelial dysfunction, therefore to a cascade of pathophysiological events of the development of PE [31]. Lipid excess and oxidative stress can provoke endothelial dysfunction. Alterations of the endothelial dysfunction may underlie the hypertension of PE [32]. In Examination of the placental transcriptome, recognized pathways affected by inflammation, lipotoxicity, and oxidative stress were amplified significantly in placenta from obese women. Besides, RNA-seq analysis recognized pronounced decrease in genes related to angiogenesis and hormone activity, in-

dicating that maternal dyslipidemia can negatively influence mitochondria leading to increased ROS production, oxidative stress and cellular dysfunction [33]. Oxidatively stressed placenta releases a number of trophoblast-derived antiangiogenic (e.g., soluble fms-like tyrosine kinase-1, soluble vascular endothelial growth factor, and soluble endoglin), and proangiogenic (e.g., placenta growth factor) factors that contribute to an exaggerated maternal inflammatory response with generalized endothelial dysfunction [34]. The total cholesterol/high-density lipoprotein ratio (TC/HDL) and the LDL/HDL ratio are two important components and indicators of vascular risk. Interestingly, in this study 32.43% of preeclamptic patients at atherogenic risk (T/HDL) > 4.5; and 35.13% of patients are defined with high-risk when LDL/HDL > 3.0 threshold was applied.

PE is characterized by disturbed extravillous trophoblast migration toward uterine spiral arteries leading to increased uteroplacental vascular resistance and by vascular dysfunction resulting in reduced systemic vasodilatory properties. Its pathogenesis is mediated by an altered bioavailability of NO and tissue damage caused by increased levels of ROS [35]. Vascular function modulated by the interference of ROS and NO. Increased ROS production seems to suppress the expression and function of endothelial NO synthase [36].

NO exhibits multiple and complex biological functions and many of its effects can be mostly attributed to its strong oxidant capacity. Thus, NO is an important mediator of immune homeostasis and host defense, and changes in its generation or action can contribute to pathologic states [37].

In this study, maternal serum NO levels were significantly low in the preeclamptic women compared to controls. NO was negatively and significantly correlated with SBP, DBP, TC, LDL, TG, LDH, AST, and CK, While, HDL and TAC showed positive and significant correlation. Several reports ascertain the decreased levels of NO in PE, and its negative correlation with body weight, systolic blood pressure and diastolic blood pressure [38] [39] [40] [41]. In contrast, Norris *et al.* (1999) reported that the production of NO was significantly higher in the uteroplacental, feto-placental, and peripheral circulation in PE compared to normotensive pregnancies. They attributed the marked increase in NO levels to compensatory mechanism to the pathological effect of PE [42].

In normal pregnancy, NO derived from endothelial nitric oxide synthase (eNOS) contributes to the maintenance of vascular tone to increase uterine blood flow [43]. An up-regulation of eNOS, resulting in increased NO production has been shown to contribute to increases in uteroplacental blood flow via changes in vascular tone [44]. In addition, there is evidence that genetic eNOS polymorphisms may affect the susceptibility to hypertensive disorders of pregnancy [45]. A study on 3 polymorphisms of the eNOS gene and the plasma nitric oxide concentrations was conducted in a population of Chinese origin from mainland China. Two variants 298Asp allele and eNOS 4a were strongly associated with higher plasma NO concentrations in pregnant women and suggested

to modulate PE susceptibility [46]. Vascular tone is altered by the interference of ROS and NO, increased ROS production seems to suppress the expression of eNOS and hence reduced production of NO [47]. In fact, several studies have shown that impaired vascular relaxation in PE has been attributed to reduced bioavailability of NO produced via endothelial NOS [48]. A reduction in the bioavailability of NO and the imbalance between ROS and antioxidant activity seem to play a critical role in endothelial dysfunction contributing to raised in blood pressure and hence pathogenesis of PE [49] [50]. NO is also a potent inhibitor of platelet aggregation and activation by both cGMP-dependent and -independent mechanisms [51]. Drugs that target various components of the nitric oxide soluble guanylylcyclase pathway can help to increase NO bioavailability, and the delivery of exogenous NO is an attractive therapeutic option [52].

Total antioxidant capacity (TAC) parameter summarizes the overall activity of antioxidants and antioxidant enzymes [53]. Evaluating oxidative stress by measuring TAC can lead to a better understanding of free radical damage in oxidative stress related diseases like PE which would be useful to identify the patients with increased risk of progression of the disease and also for monitoring and optimization of antioxidant therapy [54]. In our study, the serum level of TAC was statistically low in the preeclamptic patients compared to controls. TAC was negatively correlated with SBP, DBP, BMI, TC, LDL and LDH, while it was positively correlated with HDL and NO. Risk estimate considering antioxidants revealed that pregnant women that have low level of NO and TAC had 7.6 and 2.6 times higher risk to develop oxidative stress which in turn leads to development of PE. Study findings are in agreement with the study of Hasan and Dina (2014) who reported that the serum level of TAC was significantly low in preeclamptic cases signifying that the decrease in TAC leads to an imbalance between prooxidants and antioxidants in those women that go on to develop PE [55]. Oxidative stress reflects an imbalance between the formation of oxidative substances and the innate antioxidants that make up the endogenous defense system [56]. During normal pregnancy there is a slight increase in oxidative stress, even in the presence of antioxidant systems [57]. In PE, the abnormal vascular development of the blood vessels in the placenta leads to reduced placental perfusion and induce hypoxia which is by itself a potent stimulus for ROS formation [16].

A genome-wide transcriptomic view identified genes involved in lipid metabolism, angiogenesis, hormone activity, and inflammation to be significantly altered in placenta from obese women. These studies provide evidence for increased lipids and decreased TAC in placenta from obese women, and pinpointed key signaling pathways (increased JNK/FoxO4 signaling) and downstream mediators (HIF-1α and VEGF-A) that provide a link between maternal-obesity, placental inflammation/oxidative stress, and altered angiogenic factors. Obesity provokes cellular stress, which may in turn adversely affect placental development and function [33]. Antioxidants may be utilized to greater extent to counteract and scavenging free radicals, resulting in the reduction of

their levels [58].

The limitations of this study include the relatively small sample size. There were no follow up criteria set. Even with this limitation, the findings of this study serve as ground for further studies to better understanding the associations of total antioxidant capacity and nitric oxide levels with preeclampsia.

5. Conclusions

Women with excessive BMI change have a higher chance of developing PE. Low level of high-density lipoprotein cholesterol and high level of low-density lipoprotein cholesterol define that dyslipidemia increases the risk of PE. Decreased levels of NO and TAC might reflect the oxidative stress and likely contribute to the pathophysiological mechanisms of PE.

Recommendations

Longitudinal studies with serial measurements of biochemical markers needed to elucidate the pattern of changes and the pathophysiological consequences of such changes during pregnancy that leads to development of PE. Further studies should be conducted to consider the role of NO and TAC as important factors in the pathogenesis of PE. More studies can clarify the etiological background of PE to provide guidance for the prevention and follow-up of women who experience PE.

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