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MARKERS OF TISSUE DAMAGE AS INDICATORS OF COMPLICATIONS OF PREECLAMPSIA IN PREGNANT SUDANESE WOMEN

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ABSTRACT

Background: Preeclampsia is a pregnancy-related syndrome, which still represents one of the major causes of maternal-fetal mortality and morbidity mainly in underdeveloped countries where its incidence and mortality rates are higher. **Aim:** To evaluate the role of markers of tissue damage as indicators of complications 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 lactate dehydrogenase (LDH), aspartate aminotransferase (AST), creatine kinase (CK), uric acid, and creatinine between preeclamptic and controls. **Result and conclusion:** The study revealed an elevation in the levels of LDH (P<0.0001), AST (P= 0.029), CK (P<0.0001), uric acid (P=0.001) and creatinine (P=0.006) in preeclamptic women than controls. These levels might indicate the severity of the tissue damage in preeclamptic women.

KEYWORDS: Preeclampsia; Oxidative Stress; Hypertension; Proteinuria.

1. INTRODUCTION

Pregnancy is a temporary condition in the life of a woman that associated with many physiological changes, but when it is complicated by preeclampsia (PE) it has adverse outcomes on both pregnant and her fetus.[1]

Preeclampsia is a multisystemic disease characterized by the onset of hypertension after 20 weeks of gestation in a previously normotensive lady, with the presence of proteinuria or, in its absence, of signs and symptoms indicative of target organ injury.[2] The clinical signs and symptoms involve multiple organs, including the liver, kidneys, heart, lungs, brain, and pancreas. The complications of PE have harmful effects on both maternal and fetal that can result in intrauterine growth restriction, placental hypoperfusion, premature placental disruption or, in most serious situations, termination of pregnancy and fetal and maternal death.[3]

PE is uniquely in the pregnant patient, which is characterized by systemic inflammation, endothelial cell dysfunction, excessive thrombin generation, an anti-angiogenic state and is usually associated with multiple organ involvement.[4] However, PE is fundamentally a placental disease which manifests itself, in most cases, by involvement of the vascular and renal systems.[5]

The overall incidence of PE is 2-12%[6] and the syndrome results in more than 63,000 maternal deaths globally annually, 75% are experienced in a mild form, and 25% in a severe form.[7] Although it is a well-studied disease, PE is still a disease of theories as the exact cause remains uncertain.[8] Several key features are thought to have a role in the development of PE, which is mainly considered as a vascular disorder. The most probable causes for this disease are a failure of trophoblast invasion leading to a failed transformation of the uterine spiral arteries, and an incorrect deep placentation.[9]

Objectives of this study are to determine the serum LDH, AST, and CK as indicators of tissues damage in preeclamptic women and to measure the level of serum uric acid and creatinine for renal function assessment as consequences of PE.

2. MATERIAL AND METHODS

This was a cross-sectional (case-control) study conducted to evaluate the role of markers of tissue

damage as indicators of complications 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 97 normal pregnant women.

2.1. Inclusion criteria

Preeclamptic women with blood pressure ≥ 140/90, and proteinuria ≥300mg/24hrs 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 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 put in plain 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 LDH, AST, CK, uric acid and creatinine.

The levels of all parameters were measured using fully automated A15 chemical analyzer manufactured by Biosystems Company S.A Costa Brava30, 08030 Barcelona (Spain).

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

Table (1) shows the characteristics of preeclamptic patients and controls regarding age , gestational age, 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 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 <0.0001 and <0.0001 respectively) (Figure 2).

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 mean levels of LDH, AST and CK were significantly higher in preeclamptic women than normal pregnant women(*p*-values were <0.0001, 0.029 and <0.0001respectively). Renal function parameters, the uric acid and creatinine were significantly increased in preeclamptic women compared to the controls (*p*-values were 0.001 and 0.006 respectively). Preeclamptic women were more likely to have a risk of tissue damage compared with controls (Table 3).

Table 1: Characteristics and description of study groups.

Characteristic	Patients (N = 111)	Controls (N = 97)	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%)	0.889
Urban	47 (42.3%)	40 (41.2%)	87 (41.8%)	
Total	111 (100%)	97 (100%)	208 (100%)	
Parity				
Primiparous	54 (48.6%)	37 (38.1%)	91 (43.8%)	0.185
Multiparous	41 (36.9%)	48 (49.5%)	89 (42.8%)	
Grand multiparous	16 (14.4%)	12 (12.4%)	28 (13.5%)	
Total	111 (100%)	97 (100%)	208 (100%)	

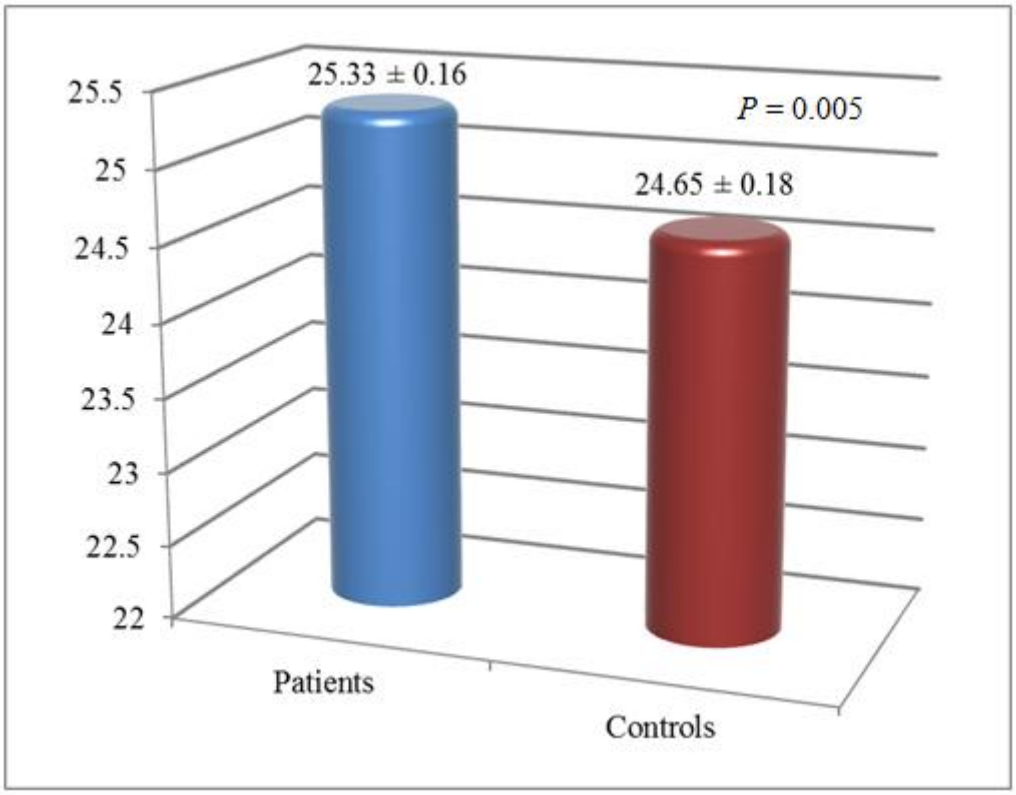

Figure 1: Body mass index of preeclamptic and control groups.

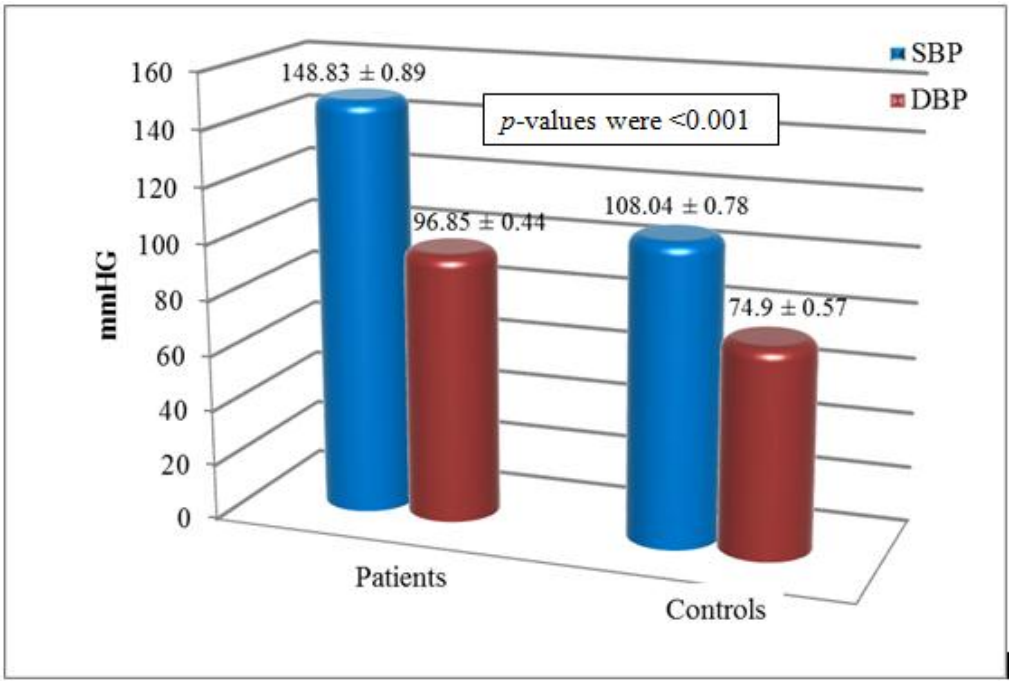

Figure 2: Blood pressure of preeclamptic cases and control group.

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

Parameter	**Patients** (N = 111)	**Controls** (N = 97)	***p*-value**
LDH	449.53 ± 23.79	345.73 ±15.09	<0.0001
AST	22.59 ± 0.95	19.56 ± 1.01	0.029
CK	70.87 ± 4.58	47.84 ± 3.68	<0.0001
Uric Acid	3.64 ± 0.16	2.99 ± 0.10	0.001
Creatinine	0.72 ± 0.02	0.64 ± 0.02	0.006

Table 3: Comparison of risk estimate considering the parameters of tissue damage between preeclamptic women and controls.

Parameter	Patients	Controls	Total	*p*-value	Chi value	OR (CI: 95%)
LDH						
Normal	65 (58.6%)	71 (73.2%)	136 (65.4%)	**0.029**	4.900	1.933 (1.075 - 3.476)
High	46 (41.4%)	26 (26.8%)	72 (34.6%)			
Total	111 (100%)	97 (100%)	208 (100%)			
AST						
Normal	105 (94.6%)	91 (93.8%)	196 (94.2%)	1.000	0.058	0.867 (0.270 - 2.781)
High	6 (5.4%)	6 (6.2%)	12 (5.8%)			
Total	111(100%)	97 (100%)	208 (100%)			
CK						
Normal	99 (89.2%)	91 (95.8%)	190 (92.2%)	0.116	3.113	2.758 (0.859 - 8.857)
High	12 (10.8%)	4 (4.2%)	16 (7.8%)			
Total	111 (100%)	95 (100%)	206 (100%)			
Uric acid						
Normal	99 (89.2%)	95 (97.9%)	194 (93.3%)	**0.013**	6.312	5.758 (1.225 - 26.409)
High	12 (10.8%)	2 (2.1%)	14 (6.7%)			
Total	111 (100%)	97 (100%)	208 (100%)			
Creatinine						
Normal	97 (87.4%)	89 (91.8)	186 (89.4%)	0.370	1.043	1.606 (0.643 - 4.009)
High	14 (12.6%)	8 (8.2)	22 (10.6%)			
Total	111 (100%)	97 (100%)	208 (100%)			

3.1. Correlation of measured parameters with uric acid

Table (4) shows the correlation of LDH, AST, CK and creatinine with uric acid. Uric acid was positively correlated with LDH (r = 0.396, p = <0.0001), AST (r = 0.318, p = <0.0001), CK (r = 0.495, p = <0.0001), and creatinine (r = 0.411, p = <0.0001).

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 complication factors what were the most significantly factors that their levels actually affected by the severity of the PE as indicated by SBP and DBP.

Because hypertension is the main clinical manifestation of PE, SBP and DBP were taken as independent variable with PE-associated complication factors (LDH, AST, CK, uric acid and creatinine) as dependent variables. 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 complication factors, the most significant PE-associated complication factor was CK (p-value is < 0.0001, β is 0.246) (Table 5). This indicate that for an increase of one unit in standard deviation of SBP the excepted increase in standard deviation of CK was 0.246.

The regression lines between SBP and BMI, CK are shown in (Figure 3).

3.2.2. Diastolic blood pressure model

From the output of the multiple linear regression for PE-associated complication factors, the most significant PE-associated complication factors were CK (p = < 0.0001, β = 0.156) and LDH (p = < 0.0001, β = 0.152) as shown in (Table 5). These results indicate that for an increase of one unit in standard deviation of DBP the excepted increase in standard deviation of CK and LDH were 0.156 and 0.152 respectively. The linear relationship between DBP and BMI, LDH and CK are shown in (Figure 4). AST, uric acid and creatinine were excluded from the model of the multiple linear regression analysis although they were significant PE-associated complication factors.

Table 4: Correlation of measured parameters with uric acid.

Parameter	Correlation coefficient (r)	*p*-value
LDH	0.396**	< 0.0001
AST	0.318**	< 0.0001
CK	0.495**	< 0.0001
Creatinine	0.411**	< 0.0001

** 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 5: Multiple linear regression analysis of the biochemical parameters associated with the complications of PE.

Dependent variable	Parameter	Un standardized coefficient		Standardized coefficient	t	*P*-value
		B	SE	β		
CK	SBP	0.123	0.034	0.246	3.631	< 0.0001
CK	DBP	0.042	0.021	0.156	2.039	0.043
LDH	DBP	0.008	0.004	0.152	1.988	0.048

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

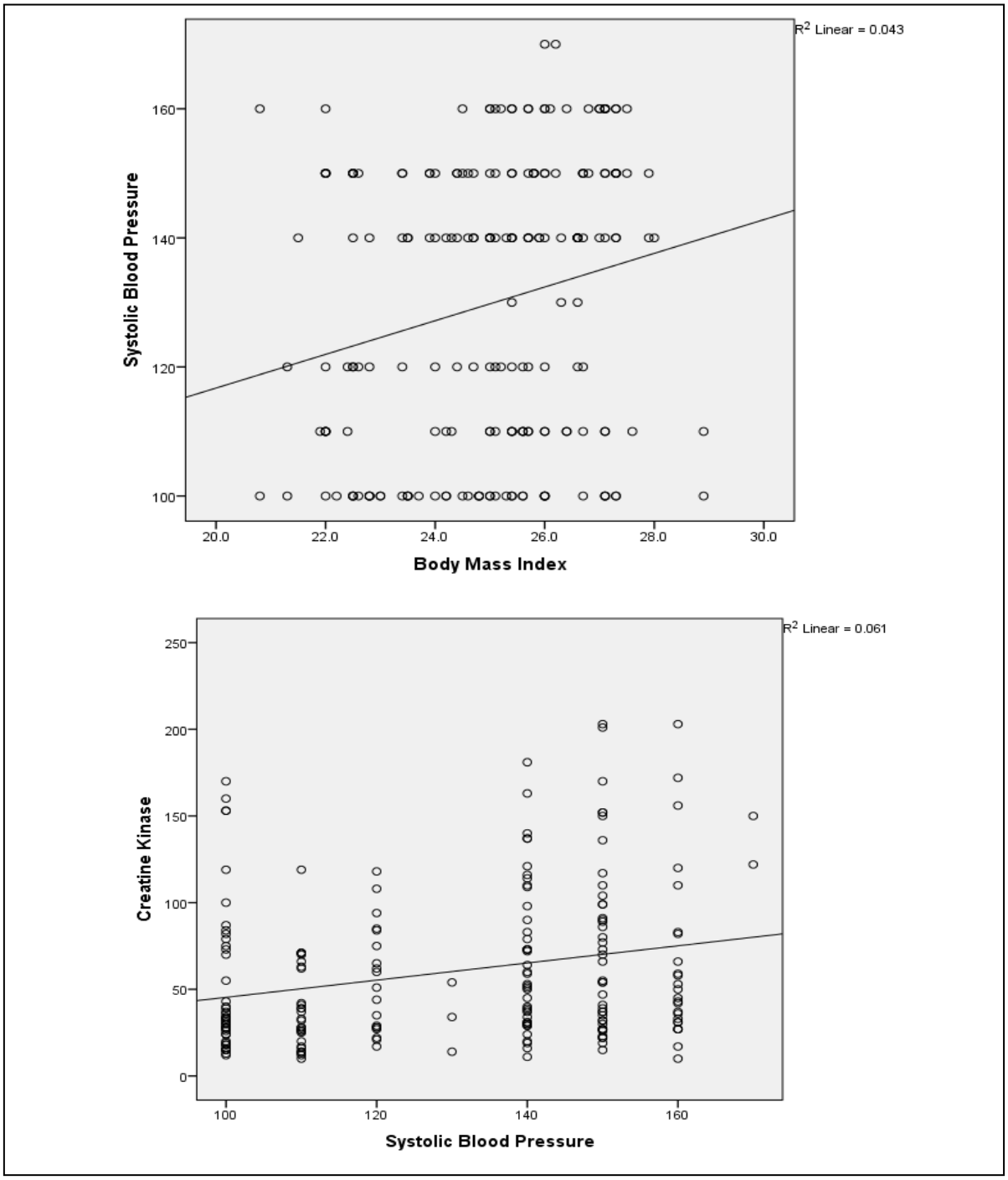

Figure 3: Linear relationship between SBP and BMI, CK.

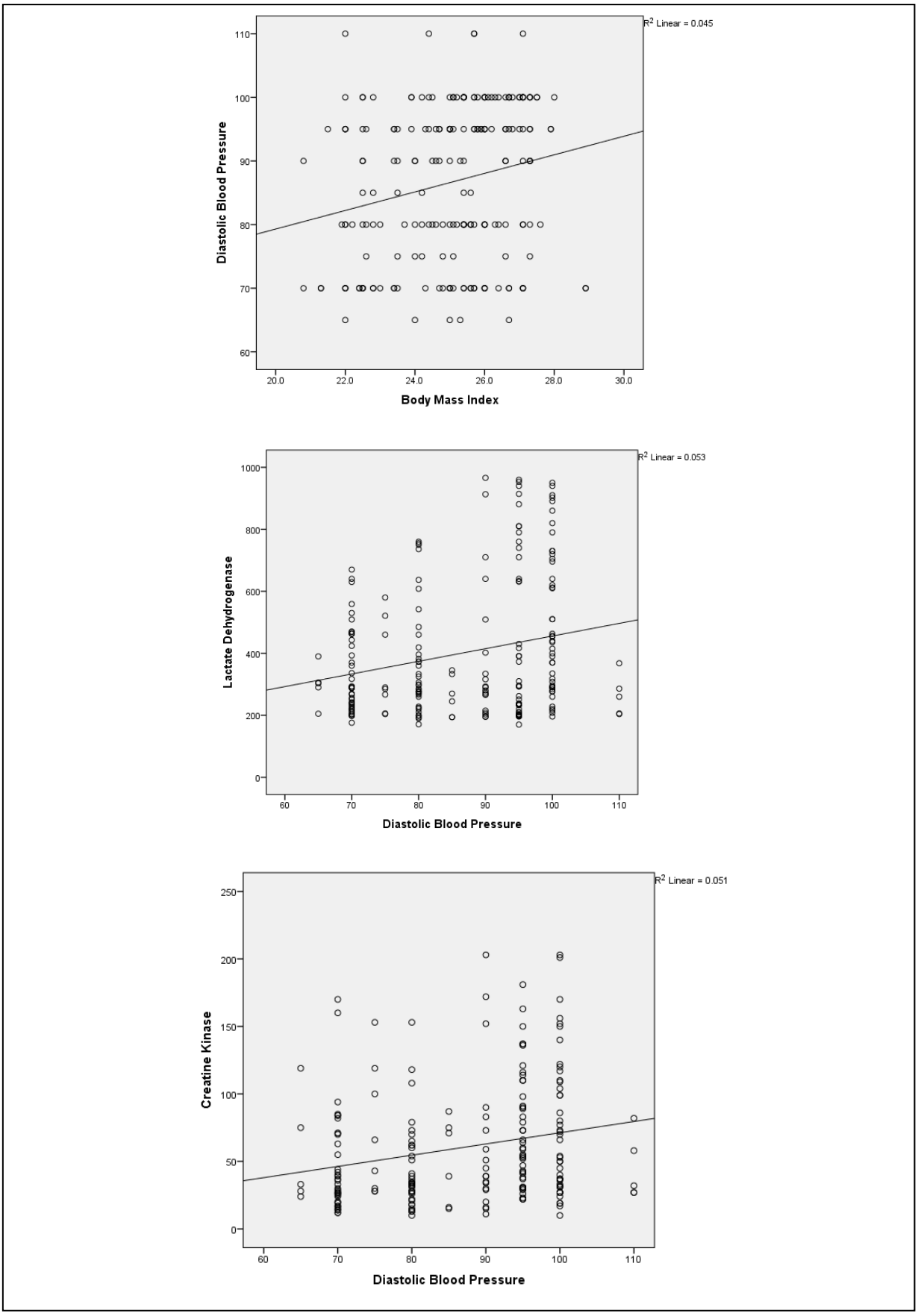

Figure 4: Linear relationship between DBP and BMI, LDH, CK.

4. DISCUSSION

Preeclampsia is a pregnancy-related disorder that is still remain among the leading causes of maternal and perinatal morbidity and mortality worldwide.

This study aimed to evaluate the role of markers of tissue damage as indicators of complications 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.

Renal injury is a common pathophysiological feature in women with preeclampsia as evidenced by increased protein leakage (proteinuria) and glomerular injury (glomerular endotheliosis).[10,11]

It has been established that hypertension during preeclampsia is associated with increased maternal vascular sensitivity to angiotensin II and agonistic autoantibodies to the angiotensin II type I receptor via activation of endothelin-1 and oxidative stress.[12] Several approaches to improve control of blood pressure were highlighted: inhibition of ANG II activity, by either blocking angiotensin II type 1 receptors or angiotensin-converting enzyme, or by preventing oxidative stress by administration of antioxidants.[13] Without a proper intervention, microvascular endothelial cell injury plays a central role in the pathogenesis of preeclampsia. On that account, end organ damage is mostly directed towards organ systems highly dependent on the microvasculature for normal function including the kidney.[14]

The excessive cellular activity associated with the process of placental ischemia leads to overproduction of uric acid which serves as a marker of the disease, with abnormal levels seen much earlier than the detection of proteinuria.[15] This study revealed that the mean serum uric acid and creatinine concentrations were significantly higher in preeclamptic women compared to controls. Uric acid concentrations showed significantly positive association with the selected markers of complications LDH, AST, CK, and creatinine. Previous studies, indicated the association of uric acid level in preeclampsia, and its insinuative function as a marker of oxidative stress providing index for early diagnosis and clinical severity of the PE.[15,16] Other reports also showed that, serum uric acid and creatinine concentrations seem to be useful parameters to predict maternal complications and the management of women with PE.[17-19] In normal pregnancy, uric acid concentration initially falls 25-35% due to elevation in renal clearance secondary to increased glomerular filtration rate (GFR) or reduced proximal tubular re-absorption due to changes in its production rate. Later in pregnancy the serum uric acid level increases possibly due to raised fetal production, altered renal function and increased activity of xanthine oxidase.[20-22]

Ischemic placenta in preeclampstic women subsequently becomes hypoxic leading to its tissue breakdown which provides an additional source of purines for generation of uric acid by xanthine oxidase.[23,24]

Furthermore, uric acid can promote endothelial inflammation, damage and dysfunction, therefore PE, which is characterized by widespread endothelial dysfunction might be promulgated by uric acid.[25] Uric acid decreases nitric oxide production by the endothelial cells due to its endothelial dysfunction action.[26] In addition, it stimulates human monocytes to produce the pro-inflammatory cytokines IL-1β IL-6 and TNF-α, which are also elevated in the circulation of experimentally induced hyperuricemic animals as well as preeclamptic women. In preeclamptic women the increased concentration of circulating TNF-α was positively related with circulating uric acid concentrations.[21]

Because during gestation there is a physiological increase in the glomerular filtration rate (GFR) and reduction of serum creatinine, even mild elevations of the latter can indicate renal function insufficiency. Severe PE can lead to deterioration of kidney function, chiefly in women with previous chronic kidney disease (CKD) and GFR below 40 mL/min/1.73m2 (< 0.67 mL/s/m2).[27] More than 70% of women who become pregnant with a serum creatinine>2.5 mg/dl will experience preterm delivery, and >40% develop preeclampsia. Women who initiated pregnancy with a serum creatinine >2.0 mg/dl had a high (33%) likelihood of an accelerated decline in renal function during or immediately after pregnancy.[28] Hence, it is reasonable to consider the concentrations of uric acid and creatinine in women with PE.

PE can affect every maternal organ, predominantly the vascular, renal, hepatic, cerebral and coagulation systems. LDH levels were significantly elevated in women with PE and eclampsia and significantly correlated with high blood pressure as well as poor maternal and perinatal outcome. Extracellular activity of LDH increases under the condition of oxidative stress, since the cell integrity can be disrupted during the lipid peroxidation process.[29] Higher serum LDH levels were associated with increased incidence of maternal complications like placental abruption, renal failure, HELLP syndrome, cerebrovascular accidents; preeclamptic women with higher LDH concentrations >800 IU/l were more likely to have complications and neonatal death.[29] In this study 35 out of 111 patients (31.53%) had moderately to highly elevated LDH levels (600–800 IU/l).

Liver may undergo periportal hemorrhagic necrosis giving rise to elevated enzyme levels.[30] In contrast to

normal pregnancy which is generally associated with normal AST, in PE AST concentrations was found to be elevated.[31] In accordance, the present study showed that the serum level of AST was significantly higher in preeclamptic women than control group. Similar findings were reported and revealed that the serum LDH and AST concentrations were significantly higher in preeclamptic patients compared to normal pregnant women and stated that LDH and AST may be increased due to liver damage.[32]

Creatine kinase (CK) is associated with high blood pressure, and it is also a better indicator of heart or muscle damage.[33] CK is a main predictor of blood pressure, and this is thought to largely depend on high resistance artery contractility.[34] LDH and CK were found to be elevated due to cellular damage in preeclamptic women, and have a significant association with various maternal complications specially cardiovascular and fetal outcomes.[29,35]

5. CONCLUSIONS

Excessive BMI change have a higher chance of developing preeclampsia. Elevation in serum levels of LDH and CK might indicate the severity of the tissue damage in preeclamptic women.

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