Biochemical and Oxidative Biomarkers in Preeclampsia

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ABSTRACT

Objective: To determine the biochemical and oxidative stress parameters as biomarkers in preeclampsia.
Study Design: Cross-sectional analytical study.
Place and Duration of the Study: Departments of Obstetrics / Gynaecology and Biochemistry, Quaid-e-Azam Medical College, Bahawalpur, Pakistan, from September 2022 to February 2023.
Methodology: Women with preeclampsia were selected based on blood pressure exceeding 140/90 mmHg and proteinuria levels exceeding 300 mg/24 hours or showing a +1 on a dipstick test. Normotensive pregnant women were selected as controls. Venous blood was taken and centrifuged, and routine biochemical methods were used to estimate serum lipid profile levels and minerals. The estimation of oxidative stress enzymes was carried out manually using special chemicals. Student's t-test and Pearson's correlation were applied to analyse the result.
Results: The study included 228 subjects: 114 preeclampsia patients and 114 normal pregnant women as controls. The mean systolic blood pressure was measured at 166.25 mmHg and the diastolic blood pressure was 92.80 mmHg ($p < 0.001$). All lipid profile estimations showed notable abnormalities, but the mean level of triglycerides (TGs) (214.90 ± 15.59 mg/dl) in preeclamptic patients was significantly elevated ($p < 0.05$). In terms of minerals, all were deranged but magnesium (1.37 ± 0.35 mg/dl) and calcium (7.55 ± 0.45 mg/dl) were significantly decreased ($p < 0.05$). All oxidative enzyme levels were increased ($p < 0.05$) but malondialdehyde (MDA) with a mean level of 2.58 ± 0.40 nmol/ml was significantly elevated. The Pearson's correlation of these parameters with blood pressure also showed a positive association.
Conclusion: Total cholesterol triglyceride in the lipid profile, calcium and magnesium in minerals, and MDA in oxidative parameters were markedly deranged and exhibited significant associations with the severity of the disease, so could be used as disease biomarkers of preeclampsia.

Key Words: *Preeclampsia, Gestational hypertension, Proteinuria, Lipid profile, Minerals, Oxidative stress.*

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INTRODUCTION

Preeclampsia is a progressive pregnancy disorder that presents as new onset hypertension after 20 weeks of gestation with one or more of the following features: Significant proteinuria or maternal organ dysfunction such as renal insufficiency, liver involvement, and neurological or haematological complications.[1] It affects 2-10% of pregnancies worldwide with an incidence of 2.4% in Pakistan.[2] It accounts for 15% of preterm birth, moreover, growth retardation, encephalopathy, and other complications of premature birth may be encountered. According to the community-level interventions for preeclampsia (CLIP) trial, 17% of maternal deaths are attributable to hypertensive disorders.[3]

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The exact cause of preeclampsia is unknown. Clinicians and researchers are developing tests and methods for early detection and diagnosis, and providing close monitoring and optimal management to minimise its negative consequences.

Numerous theories explain the aetiology and pathogenesis of preeclampsia, with the widely accepted two-stage model, suggesting improper placentation and both maternal and foetal factors. These factors alter maternal systemic endothelial function, causing an exaggerated inflammatory response and oxidative stress.[4] This systemic inflammation and oxidative stress lead to the formation of reactive oxygen species (ROS) and reactive nitrogen species (RNS). When ROS or RNS combine with nitric oxide (NO), they form peroxynitrite, a harmful molecule that can cause cell destruction and endothelial cell death.[5]

An imbalance between lipid peroxidation and antioxidant mechanisms in preeclampsia impairs normal endothelial function.[6] This occurs when low-density lipoprotein (LDL) is oxidised by ROS in arterial intima micro-domains, converting LDL into foam cells that cause vascular endothelial damage. Oxidative stress and lipid peroxidation are central to the placental and endothelial dysfunction, leading to hypertension and other preeclampsia complications.[7] Changes in lipid profile and lipid peroxidation are positively correlated with endothelial dysfunction, with triglycerides (TGs),

total cholesterol (TC), and low-density lipoprotein-cholesterol (LDL-C) levels showing a marked rise in preeclampsia compared to a normal pregnancy.[8]

Electrolytes play a crucial role in regulating blood pressure, and their disruption can cause vessels to become hyper-responsive to vasoconstrictors such as vasopressin and antidiuretic hormone (ADH), leading to hypertension in preeclampsia.[9] An imbalance in sodium (Na) and potassium (K) levels contributes to the development of preeclampsia.[10] Additionally, magnesium is believed to alter angiogenic and inflammatory responses, leading to decreased vascular contraction and reduced hypertension in preeclampsia.[11] Women with preeclampsia have impaired calcium and magnesium homeostasis and metabolism.[12]

Timely detection of these parameters can help healthcare professionals intervene in the disease progression to complicated preeclampsia and appropriately manage symptoms of the disease. The present study aimed to estimate biochemical and oxidative biomarkers in the population of Southern Punjab, Pakistan.

METHODOLOGY

A cross-sectional analytical study was conducted at the Quaid-e-Azam Medical College / Bahawal Victoria Hospital, Bahawalpur, after obtaining ethical approval from the Institutional Review Board. The study included 228 subjects: 114 preeclampsia patients and 114 normal pregnant women as controls from the Obstetrics and Gynaecology Department. Preeclampsia was identified by blood pressure over 140/90 mmHg and proteinuria levels exceeding 300 mg/24 hours or a +1 on dipstick test. Hospitalised individuals were approached directly, and sociodemographic information was gathered from both patients and their attendants. Data collection followed a consecutive sampling method based on inclusion and exclusion criteria. Women aged 20 to 45 years with singleton pregnancies, who developed hypertension (SBP >140 mmHg or DBP >90 mmHg on two occasions 6 hours apart) and proteinuria (>300 mg/24 hours or +1 on dipstick) during pregnancy, were included. Exclusions were made for women with chronic hypertension, gestational diabetes, cardiovascular disorder, renal disease, immunological disorders, PCOS, metabolic disorders, multiple pregnancies, or incomplete information. Written informed consent was obtained from all participants and confidentiality was maintained.

A 5 ml blood sample was collected from the median cubital vein using aseptic techniques and transferred to vacutainers without additives. After centrifugation at 3000 rpm for 10 minutes, serum was separated and stored in Eppendorf tubes at -20°C. Serum lipid profile and Ca^{++} and Mg^{++} levels were measured using a Beckman coulter AU-680 chemistry analyser through the spectrophotometric method. Serum electrolytes were analysed using an Easylyte analyser with the ion-selective electrode (ISE) potentiometer method. Oxidative stress enzyme levels were determined manually following protocols by different scientists. The lipid peroxidation marker MDA (2.02-4.65 nmol/ml) was assessed using Ohkawa's procedure and catalase levels (0.1-1.0 µmol/ml) were estimated using Aebi's method.[13] Glutathione peroxidase (Glt-Px, 1.1-8.7 mg/ml) was measured following Tietze's enzymatic recycling protocol. The Kakkar's method determined superoxide dismutase (1.3-3.5 ng/ml).[14] All tests were personally performed by the principal investigator in the Pathology / Biochemistry Laboratory at the Quaid-e-Azam Medical College / Bahawal Victoria Hospital, Bahawalpur, with costs covered by the authors.

The data were analysed with the help of SPSS version 25.0. Mean and standard deviation (SD) were calculated for quantitative variables that were normally distributed. For qualitative variables, frequencies and percentages were given and presented in tabular form. Student's t-test was performed to compare both groups. A 95% confidence interval was calculated. Pearson's correlation was applied between the clinical / demographic and biochemical parameters of the participants. The results were considered significant when the p-value was less than 0.05.

RESULTS

This study showed significant variation in demographic, biochemical, and oxidative parameters. The findings (mean ± SD and 95% CI) of these parameters are summarised in Table I.

Table I: Mean (SD) and 95% CI of the biochemical and oxidative parameters of preeclampsia subjects and normotensive pregnant women.

Parameters	Control (114)			Cases (114)			p-value
	Mean ± SD	95% CI		Mean ± SD	95% CI		
		Upper	Lower		Upper	Lower	
Demographic characteristics							
Age (years)	30.0 ± 5.78	31.084	28.916	27.82 ± 6.36	29.012	26.628	0.007
Gestational age (weeks)	30.21 ± .32	30.842	26.628	31.45 ± 2.81	31.988	30.932	0.003
Weight (Kg)	74.04 ± 7.06	71.362	68.718	81.63 ± 8.00	83.128	80.132	<0.001
BMI	26.83 ± 3.16	27.422	26.238	29.51 ± 2.96	30.076	28.964	<0.001
SBP (mm/Hg)	124.99 ± 3.12	125.574	124.406	166.25 ± 11.21	168.352	164.148	<0.001
DBP (mm/Hg)	83.64 ± 1.80	83.988	83.312	92.80 ± 6.55	94.038	91.582	<0.001
Lipid profile and LDH estimation							
Cholesterol (mg/dl)	174.88 ± 13.50	177.418	172.362	210.14 ± 20.40	213.962	206.318	<0.05
Triglyceride (mg/dl)	184.65 ± 12.30	186.992	182.328	214.90 ± 15.59	218.806	210.994	<0.05
LDL (mg/dl)	70.92 ± 2.62	73.224	68.616	101.78 ± 2.72	104.700	98.86	<0.05
HDL (mg/dl)	40.08 ± 12.45	40.58	39.6	36.23 ± 20.85	36.75	35.73	<0.05
Estimation of oxidative stress parameters							
MDA (nmol/ml)	0.92 ± 0.12	0.951	0.904	2.58 ± 0.40	2.658	2.50	<0.05
Catalase (µmol/mol)	1.19 ± 0.09	1.206	1.174	1.70 ± 0.14	1.726	1.674	<0.05
SOD (ng/ml)	1.70 ± 0.05	1.708	1.692	2.56 ± 0.25	2.606	2.514	<0.05
Glt-Px (mg/dl)	1.51 ± 0.37	1.581	1.44	3.20 ± 0.32	3.264	3.141	<0.05
Estimation of minerals and electrolytes							
Mg (mg/dl)	2.40 ± 0.25	2.449	2.357	1.37 ± 0.35	1.432	1.302	<0.05
Ca (mg/dl)	8.69 ± 0.54	8.796	8.595	7.55 ± 0.42	7.632	7.474	<0.05
Na (mEq/L)	137.35 ± 3.04	137.928	136.792	147.55 ± 4.26	148.348	146.752	<0.05
K (mEq/L)	3.78 ± 0.26	3.834	3.737	3.15 ± 0.37	3.192	3.052	<0.05

Student's t-test was applied to compare the means of the two groups.

Table II: Pearson's correlation of demographical / clinical parameters with biochemical and oxidative parameters.

Parameters		Age		Gest. Age		BMI		S-BP		D-BP	
		r	p-value	r	p-value	r	p-value	r	p-value	r	p-value
Cholesterol	Case	-0.042	0.654	-0.131	0.166	0.144	0.127	0.213*	0.023	0.189*	0.023
	Cont.	0.720	0.449	-0.049	0.607	-0.131	0.165	-0.082	0.385	0.028	0.767
TG	Case	0.049	0.604	0.243**	0.009	0.011	0.910	0.368**	<0.001	0.276**	0.001
	Cont.	0.480	0.610	0.206*	0.028	0.019	0.839	0.016	0.865	-0.050	0.595
LDL-C	Case	0.086	0.365	0.085	0.369	0.106	0.261	0.121	0.199	0.166	0.017
	Cont.	0.750	0.425	-0.169	0.072	0.100	0.290	-0.179	0.057	0.032	0.811
HDL-C	Case	-0.009	0.925	0.186*	0.048	0.049	0.608	0.019	0.838	0.021	0.827
	Cont.	0.180	0.851	0.098	0.300	-0.580	0.538	-0.165	0.080	0.053	0.575
MDA	Case	0.021	0.822	0.835**	<0.001	0.408**	<0.001	0.190*	0.043	0.210*	0.025
	Cont.	-0.047	0.620	0.680**	<0.001	-0.016	0.870	0.131	0.163	-0.145	0.123
SOD	Case	0.015	0.873	0.753**	<0.001	0.344**	<0.001	0.166	0.077	0.009	0.923
	Cont.	-0.187*	0.046	0.114	0.226	-0.035	0.718	-0.151	0.108	0.044	0.639
Catalase	Case	0.006	0.951	0.012	0.896	0.267**	0.004	0.043	0.699	-0.110	0.245
	Cont.	-0.235	0.012	0.080	0.399	0.003	0.973	0.013	0.888	-0.016	0.870
Glt-Px	Case	-0.050	0.959	0.247	0.008	0.169	0.073	0.021	0.828	0.175	0.063
	Cont.	0.173	0.066	-0.105	0.268	0.159	0.091	-0.011	0.911	-0.074	0.435
Na	Case	0.083	0.378	0.286**	0.000	0.030	0.754	-0.118	0.181	-0.121	0.827
	Cont.	0.162	0.086	0.222	0.018	-0.024	0.799	-0.037	0.585	-0.179	0.057
K	Case	0.081	0.394	-0.483**	0.000	-0.278*	0.003	-0.187	0.181	-0.107	0.257
	Cont.	0.050	0.600	0.235**	0.002	0.031	0.746	-0.007	0.941	0.109	0.248
Mg	Case	0.079	0.404	-0.555**	<0.001	-0.222*	0.017	-0.134	0.157	-0.169	0.081
	Cont.	0.034	0.721	-0.148	0.115	0.056	0.554	0.036	0.702	0.180	0.055
Ca	Case	0.005	0.957	0.028	0.768	0.024	0.801	0.368**	0.000	0.290**	0.002
	Cont.	-0.007	0.943	-0.038	0.692	-0.097	0.306	-0.064	0.499	0.081	0.390

**Slightly significant, **highly significant.*

Pearson's correlation analysis revealed significant associations within various parameters across different domains. Detailed correlations are delineated in Table II.

DISCUSSION

The comprehensive assessment of lipid profile including TC, TGs, LDL-C, and HDL-C levels, alongside essential minerals such as sodium, potassium, magnesium, and calcium, underscores the multifactorial nature of preeclampsia. Furthermore, the investigation into antioxidant enzymes, including malondialdehyde (MDA), superoxide dismutase, catalase, and glutathione peroxidase levels, sheds light on the oxidative stress component inherent in this pregnancy-related disorder.

Considering lipid profile preeclamptic pregnant women in the present study had considerably lower HDL-C levels ($p < 0.05$) than normal pregnant women. This finding relates with several other research studies conducted worldwide. In a population-based study conducted in Australia, it was discovered that preeclampsia patients had lower HDL levels than typical pregnant women.[15] Results from a different study carried out in Africa were comparable as well.[16] In the present study, the concentrations of TGs, LDL-C, and TC were shown to be considerably higher in preeclamptic women than in normal pregnant women. According to a study by Kockx *et al.*, preeclamptic patients had considerably higher blood TGs and free fatty acids levels.[15] Tesfa *et al.* also demonstrated a link between preeclampsia and elevated TG and LDL-C levels in the African population.[16] Bhat *et al.* revealed similar findings in the Indian population.[17] Li *et al.* also revealed similar results in the Chinese population.[18] Pearson's correlation between clinical and biochemical parameters indicated that gestational age exhibits a positive correlation with TGs in both cases and controls, while systolic blood pressure (SBP) and diastolic blood pressure (DBP) demonstrate significant positive correlations with TC and TGs specifically in the case group. A study by Ebogo-Belobo *et al.,* conducted in Africa, and Ephraim *et al*. in Ghana, showed that TC and LDL-C are associated with blood pressure, indicating a complex interplay of lipid parameters in the endothelial damage associated with disease pathogenesis.[7,8]

In the present investigation, all the oxidative stress enzymes (MDA, SOD, catalase, and glutathione peroxidase) were elevated in preeclampsia patients as compared to the controls. This increase indicates elevated oxidative stress since it shows that preeclampsia is associated with significant persistent lipid peroxidation. A study by Gohil *et al.* in India showed similar results.[19] Alkuraishy *et al.* revealed considerable increases in MDA levels in preeclampsia.[20] Decreased glutathione levels were seen in the study conducted by Ahmad *et al*.[21] Lin *et al.* in China described the elevated SOD levels as a predictive feature of preeclampsia.[22] In the present study, the Pearson's correlation analysis revealed a significant association of MDA with blood pressure. Yanglem *et al.* revealed the similar findings.[23]

Discussing electrolyte levels in the present study, magnesium, calcium, and potassium were decreased while sodium was increased in preeclampsia patients as compared to the controls. A study in the Indian population by Basavaraj *et al*. also found the similar results.[24] The decreased levels of calcium and magnesium were also reported by Aslam *et al.* in preeclamptic patients in the South-Punjab region of Pakistan.[25] Pearson's correlation analysis showed a significant correlation of calcium and magnesium with blood pressure measurements, thus indicating their association with the severity of the disease. Similar findings were reported by Al-Jamil *et al.* in the Saudi population.[9]

Although the study has identified notable findings, it also has certain limitations such as being conducted in a single hospital. This may not represent the entire Pakistani population, potentially leading to ethnic bias. Additionally, the oxidative stress tests used are costly and not widely accessible.

CONCLUSION

The study indicates significant alterations in lipid profile, minerals, and oxidative stress in preeclampsia patients. Specifically, TC and TGs within the lipid profile, calcium (Ca) and magnesium (Mg) among minerals, and MDA as an oxidative stress marker, all showed a significant association with blood pressure. These findings suggest that these parameters could serve as potential biomarkers for preeclampsia.

ETHICAL APPROVAL:
Ethical approval was obtained from the Institutional Review Board and Ethical Committee of the Quaid-e-Azam Medical College, Bahawalpur, Pakistan, vide letter no. 1800/DME/ QAMC, Dated: 13-July-2022.

PATIENTS' CONSENT:
Informed consent was obtained from all the patients.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
MNN, UM, NS, SY: Concept of the study, study design, data collection, draft of the manuscript, statistical analysis, data interpretation, and literature search.
All authors approved the final version of the manuscript to be published.

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