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Original Article

Serum Iron, Copper and Zinc Levels In Preeclampsia and Normotensive Primigravida Females

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ABSTRACT

Hypertensive ailments of pregnancy are major health problems for women and their babies around the world. Among the hypertensive disorders, preeclampsia and eclampsia are the major risk factors for maternal and neonatal morbidity and mortality. Now preeclampsia is considered a state of oxidative stress, in which over utilization of antioxidants may proceed into worst form of this disease**. Objective:** of this study was planned to assess the role of serum iron, copper and zinc as co factors for antioxidant system, and compare their levels within primigravida normotensive pregnant women and preeclampsia women. **Methods:** It was a cross-sectional comparative study conducted in Biochemistry department, University of health Sciences, Lahore. The study was carried out on 90 women which were divided into two equal groups of 45 each, preeclampsia and controls respectively. Serum levels of iron, copper and zinc were estimated by atomic absorption spectrometer. Data analyses were performed by utilizing SPSS version 20.0. **Results:**Serum levels of Fe and Cu were raised in preeclampsia patients, 151.85±61.22 (µg/dl), 130.83±48.29 (µg/dl) and serum Zn levels were decreased 77.94±23.55 (µg/dl) when compared with normotensive controls 104.39±55.36 (µg/dl), 116.64±26.56(µg/dl), and 92.77±22.91(µg/dl) respectively. A positive correlation between copper and systolic blood pressure (r= 0.440), BMI and weight (r = 0.543), while negative correlation of iron with zinc (r = -0.285) was observed in preeclamptic women. A negative correlation between copper and zinc (r = -0.440) was also observed in normal pregnant women but no such correlation was observed within Preeclampsia group. **Conclusion:** It is apparent from this study that increased levels of iron and copper and decreased levels of zinc during pregnancy is associated with the pathogenesis of preeclampsia.

INTRODUCTION

Preeclampsia and eclampsia are the major risk factors for maternal and neonatal morbidity and mortality [1]. It is found that deaths from preeclampsia and eclampsia were 300 times more in less developed countries than in more developed countries. The pathogenesis of PE differs from woman to woman depending on the underlying risk factors. Therefore, it is important to identify the different risk factors that may predispose women to PE, such as nulliparity, family history of preeclampsia, diabetes, and increase in body mass index, maternal age, kidney disease and hypertension when booking the case. In case of suspicion, the doctor is supposed to take into account the patient's antecedents, advise the urine (proteins) and blood (hemoglobin) tests, measure the height and look for edema [2]. Pakistan is ranked sixth most populous country. In a recent survey for global mortality, Pakistan ranked third among the countries most affected by maternal, neonatal and juvenile mortality [3]. The prevalence of preeclampsia represents about 3 to 10% of all pregnancies in less developed countries [4,5]. Numerous etiological

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hypotheses of preeclampsia have been suggested and widely studied. Many factors contribute to its etiology are immunologic factors, obesity, dietary factors, genetic factors, preexisting maternal pathology and antiphospholipid antibody syndrome [6]. Now preeclampsia is considered a state of oxidative stress, in which over utilization of antioxidants may proceed into worst form of this disease [7]. Free iron acts as a pro-oxidant in the body. Oxidative stress and pathological conditions cause iron to undergo a Fenton and Haber-Weiss reaction to produce reactive oxygen species, which damage biological macromolecules. During preeclampsia, free radicals are released from the damaged placenta and react with excess iron. Lipid peroxidation of cell membranes and lipoproteins begins when excess free iron reacts with their membranes. This modifies the serum activities of ferritin, transferrin, TIBC and ceruloplasmin. The end results are endothelial dysfunction, hepatic dysfunction and increased vascular resistance [8]. In addition to Iron serum copper is also an essential cofactor for several antioxidant enzymes such as catalase, Cu / Zn SOD and cytochrome oxidase, thus contributing to the antioxidant defense system. Copper acts as a pro-oxidant and can generate a reactive hydroxyl radical by participating in a single electron transfer reaction, thus contributing to oxidative stress during preeclampsia [6]. The copper transporter (CTR1) transfers copper through the placenta and is bound to iron transport by an unknown mechanism [9]. Ceruloplasmin is a copper binding protein with ferroxidase properties. Ceruloplasmin level rises during pregnancy due to increased levels of estrogens and in response to increased lipid peroxidation [10]. Another reason for this increase is due to blockade in the transfer of copper to the fetus by the placenta [11]. Copper acts as a pro-oxidant and can generate a reactive hydroxyl radical by participating in a single electron transfer reaction, thus contributing to oxidative stress during preeclampsia [8]. Therefore, the role of copper (Cu) is both pro-oxidant and antioxidant [11]. Zinc is also considered as an antioxidant because it is cofactor of superoxide dismutase enzyme which protects against free radical damage. Zinc counteracts oxidation by linking the sulfhydryl group in proteins and occupying iron and copper binding sites in lipids, proteins and DNA. Some studies have shown that a decrease in zinc concentration during pregnancy can cause fetal problems such as fetal malformations, premature labor, and maternal problems such as preeclampsia and bleeding after childbirth [12]. The accessible literature shows that oxidative stress is the consequence of an excess of reactive oxygen species. So, we can say that oxidation reduction reactions have far reaching effects and role in pregnancy and its related pathologies like eclampsia and pre-eclampsia.

METHODS

It was a comparative cross-sectional study. The study was conducted in Department of Biochemistry from March 2017 to March 2018 at University of Health Sciences, Lahore. The current study was approved from Advanced Studies and Research Board (ASRB) and Ethical Review Board, University of health Sciences Lahore. This study was conducted according to the principles expressed in the Declaration of Helsinki. Samples were collected using convenient sampling method. A total of 90 study participants were recruited from Lady Wallington Hospital Lahore and Services Hospital, out of them 45 were preeclamptic pregnant females (Group A) according to inclusion criteria (the females were primigravida, age 20 to 35 year, gestational age 30-34 weeks, blood pressure ≥ 140/90 after 20 weeks of gestation and proteinuria ≥300mg/24hr urine sample or 1+ on dipstick), and 45 were normal pregnant females (Group B) (the females were primigravida with normal blood pressure, gestational age 30-34 weeks and absence of proteinuria). The exclusion criteria were strictly followed (patients with severe anemia, hepatic and renal dysfunction, diabetes mellitus, chronic inflammatory disease was excluded). Informed written consent was given by all participants in the study. Blood pressure of all participants was measured by mercury sphygmomanometer. BMI of all the participants was calculated. Serum Zinc (Zn), copper (Cu) and iron (Fe) were measured on an atomic absorption spectrophotometer (Hitachi Z2000) with a polarized Zeeman atomic absorption spectrophotometer flame. The data was entered and analyzed by using IBM SPSS (Statistical Package for Social Sciences) version 22.0. Mean ± Standard Deviation (SD) was given for normally distributed quantitative variables and Median and Inter Quartile Range (IQR) was given for non-normally distributed quantitative variables. In case of normally distributed quantitative variables, Student "t" test was applied to compare group means with each other. In case of non-normally quantitative variables, non-parametric statistics i.e., Mann-Whitney U test was used to compare various variables between two groups. Pearson correlation (r) was used to observe correlation between normally distributed quantitative variables and Spearman's rho correlation (rho) was used to observe correlation between non-normally distributed quantitative variables. A p-value of < 0.05 was considered statistically significant for all purposes.

RESULTS

In this study, age of preeclampsia (PE) primigravida females was 25.26±3.71 (Mean±S.D) years, while in control group it was 24.06±2.34 years. The median (IQR) gestational

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age in preeclampsia group and control group was 33(32-35) and 34(32-35) months respectively, showing that most of the PE females seeking medical care were pregnant of 32 to 35 weeks. The mean levels of systolic blood pressure (114.33±7.03), diastolic blood pressures (75.11±6.52) were normal in the control group and were very high in PE group,155.11±11.20mmHg and 99.77±6.82mmHg respectively (Table 1). Significant positive correlation (p=0.002) was observed between SBP and DBP in PE females (Table-2) and also in control pregnant females (p=0.012) (Table-2), indicating simultaneous increase of SBP and DBP in study groups (Figure-2). BMI was higher in PE group 28.42±1.45kg/m2 when compared with control group 27.57±2.4kg/m2 (p=0.046) (Table-1). Significantly higher serum iron levels (p=0.000) were observed in preeclampsia group (151.85±61.22 µg/dl) as compared to healthy pregnant group (104.39±55.36 µg/dl) (Table-1), also iron was negatively correlated (p=0.058) with zinc in PE females (Table-2) while no such correlation was found in control group (Figure-1). Results of current study showed clinically raised serum Cu levels in PE females 124.52(96-163.9µg/dl) (Median along with IQR) compared to normal pregnant females 113.67(96-135µg/dl) (Table-1), but the difference of serum copper between two groups was not statistically significant (p=0.317). We found significant positive correlation (P=0.002) of copper with systolic blood pressure (Table-2,Figure-1). Results of current study showed significant lower (p=0.003) serum zinc levels (Mean±S.D) in PE group (77.94±23.55 µg/dl) as compared to control group (92.77±22.91 µg/dl) (Table-1). A positive correlation of zinc was observed with age in control group (r=0.408, p=0.005) (Table-2) and negative correlation in preeclampsia group (r=-0.064, p=0.674)(Table-2). We also observed negative correlation of zinc with copper in control group (r=-0.440, p=0.002) (Table-2) and positive correlation in patient group (Figure-1).

Parameters	Patients (n = 45)		Controls (n = 45)		p-value
	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)	
BP systolic (mm of Hg)	155.1±11.2	150 (145-160)	114.3±7.0	110 (110-120)	0.000†
BP diastolic (mm of Hg)	99.7±6.8	100 (95-104)	75.1±6.5	70 (70-80)	0.000*
BMI (Kg/m2)	28.4±1.4	28.3 (27.3-29.67)	27.5±2.4	27.91 (25.46-28.88)	0.046†
Iron (µg/dl)	151.8±61.2	147.70 (98-196.8)	104.3±55.3	98.82 (64.4-139.5)	0.000†
Copper (µg/dl)	130.8±48.2	124.52 (96-163.9)	116.6±26.5	113.67 (96-135)	0.317*
Zinc (µg/dl)	77.9±23.5	81.39 (58.6-92.8)	92.7±22.9	93.88 (82.7-107.2)	0.003†

Table-1: Comparison of all parameters in preeclampsia group (n=45) and control group (n=45).

*P value generated by Mann-Whitney U Test
† P-value generated by Independent Sample "t"-Test
P-value ≤ 0.05 is considered statistically significant

Correlation matrix of demographic and laboratory data in preeclampsia patients										
Parameters	Vale	Age	G age	SBP	DBP	Pulse	BMI	Iron	Copper	Zinc
DBP	r / rho	0.023[b]	0.177[b]	0.515**[b]						
	p-value	0.897	0.245	0.000	1					
BMI	r / rho	0.166[a]	0.134[a]	0.073[a]	0.005[a]	0.140[a]				
	p-value	0.275	0.382	0.636	0.973	0.360	1			
Iron	r / rho	0.240[a]	0.134[a]	0.238[a]	0.132[a]	-0.05[a]	-0.10[a]			
	p-value	0.112	0.381	0.115	0.386	0.745	0.502	1		
Copper	r / rho	-0.12[b]	-0.18[b]	0.44**[b]	0.08[b]	0.28[b]	0.119[b]	-0.18[b]		
	p-value	0.397	0.213	0.002	0.577	0.056	0.435	0.223	1	
Zinc	r / rho	-0.06[a]	0.049[a]	-0.016[a]	-0.06[a]	-0.06[a]	0.17[a]	-0.25[a]	0.122[a]	
	p-value	0.674	0.747	0.916	0.665	0.620	0.243	0.058	0.427	1
Correlation matrix of Demographic and laboratory data in healthy controls										
DBP	r / rho	0.073[b]	-0.2[b]	0.37*[b]	1					
	p-value	0.634	0.09	0.01						
BMI	r / rho	0.210[a]	0.06	0.32*[a]	0.187[a]	0.35*a	1			
	p-value	0.166	0.65	0.03	0.219	0.01				
Iron	r / rho	-0.07[a]	0.29[a]	-0.04[a]	-0.08[a]	0.08[a]	0.12[a]	1		
	p-value	0.622	0.05	0.79	0.568	0.57	0.40			
Copper	r / rho	-0.14[a]	0.08[a]	0.02[a]	-0.04[a]	0.08[a]	0.14[a]	-0.06[a]		
	p-value	0.362	0.60	0.87	0.779	0.58	0.34	0.65	1	
Zinc	r / rho	0.41**[a]	-0.10[a]	0.01[a]	-0.03[a]	-0.00[a]	-0.16[a]	-0.16[a]	-0.4*[a]	1
	p-value	0.00	0.51	0.91	0.843	0.96	0.28	0.28	0.00	

Table-2: Correlation matrix of demographic and laboratory data in preeclampsia patients and Healthy Controls

aCorrelation coefficient (r) and p -values are generated by Pearson Correlation coefficient
bCorrelation coefficient (rho) and p -values are generated by Spearman's Rho Correlation coefficient
p -value ≤ 0.05 is considered statistically significant
*correlation is significant at the 0.05 level (2-tailed)
** correlation is significant at the 0.01 level (2-tailed)

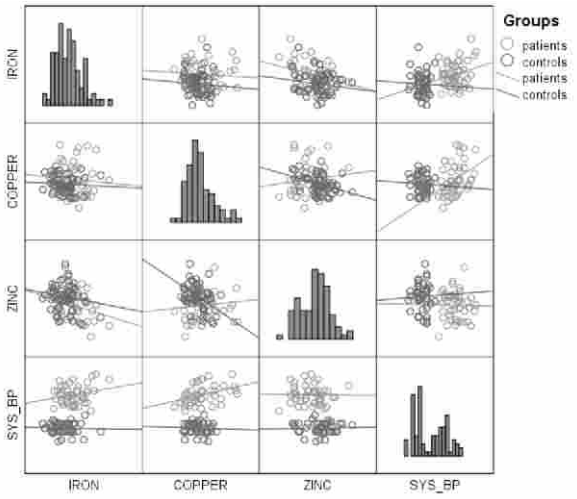

Figure-1: Scattered plots showing significant correlation of Serum Iron, Copper, Zn and Systolic Blood Pressure

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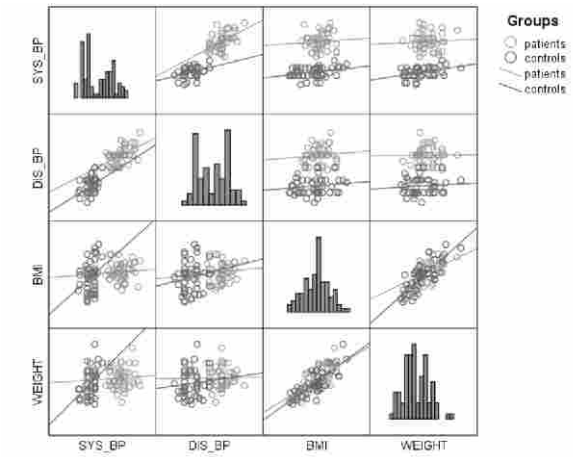

Figure-2: Scattered plots showing significant correlation of Weight, BMI, Systolic Blood Pressure and diastolic BP

DISCUSSION

Many studies have been conducted to evaluate iron levels in pregnancy and its possible contributory role in oxidative stress of PE but there were different and ambiguous results had been obtained [8]. In our study, we observed significantly higher serum iron levels in preeclampsia group as compared to healthy pregnant females. Our findings were in agreement with studies in Saudi Arabia, Bangladesh, UK, Iraq, Crotia and Korea [13-18]. It is well known that free iron act as prooxidant. It undergoes Fenton reaction to generate reactive oxygen species (ROS) and react with cell membranes and lipoproteins thus initiating lipid peroxidation. So in PE there is a possibility of placental-endothelial vasospasm which results into red bloood cells (RBCs) hemolysis leading to raised serum iron levels [8].In contrast to the present study Sarwar, M. et al. and Ahsan T. et al. in 2013 from Bangladesh, reported decreased Fe levels were observed in PE women [4,19]. The possible reason of this contradiction with our studies may be due to differences in conditions like duration of PE, severity of disease, nutritional deficiency and hemoglobin levels in PE women or some genetic and geographic variations of disease among different populations. The Cu levels are variable and contrasting in PE females. It may be due to differences in study populations, demographic variations or heterogeneity of PE or copper status of women at the time of conception, during earlier and terminal stages of the pregnancy [4]. The current study showed raised serum Cu levels in preeclampsia females compared to normal pregnant females but the difference of serum copper between two groups was not statistically significant. The results of the present study were comparable to previous studies from Iran [20]. and Sudan [21] in which no significant association of copper was observed with PE. Although a study from Turkey, showed significantly raised serum copper in PE females as compared to healthy pregnant females [22]. The variations in copper levels in different studies may be due to demographic variables or different reference range of copper level in their population. According to a studies from Iran, serum copper levels were high in PE as compared to Normal controls [23-25]. It is presumed that high copper levels are due to mobilization of Cu from maternal tissues due to increased estrogen in pregnancy. In pregnancy, ceruloplasmin levels are increased in response to higher estrogen and progesterone, which bind and carry Cu [12]. Ceruloplasmin oxidizes iron and consequently helps its binding to transferrin. It also inhibits free radical oxidation by utilizing itself as antioxidant and its rapid increase in inflammatory reaction have provided the basis for its consideration as acute phase protein(25). Contradictory to put study, lower serum copper levels were also reported in various studies in PE [4,26,7]. The potential reasons for copper damage may be associated with hormonal, metabolic, enzymatic and dietary changes in PE patients. We observed negative correlation between copper and iron in this study. Iron and copper interact with each other due to their positive charge, similar atomic radii and common metabolic fates [28]. Therefore, when level of one of them increases, the other will decrease. In our study iron levels were much increased in peeclampsia females compared to copper levels. In this study we found significant positive correlation of copper with systolic blood pressure (SBP). Similarly, the studies done by Sarwar, M in 2013 also, showed significant positive correlation of copper with SBP [4]. We can say that raised copper levels has some role in raising systolic blood pressure. A significant lower serum zinc levels in preeclampsia group as compared to control group was observed in current study. The results of present study are consistent with a study from Iran in which serum zinc levels were significantly low in PE patients as compared to controls [26].According to another study from Turkey, serum zinc levels in PE females were low as compare to healthy controls [22]. Several possible mechanisms have been put forward to explain maternal zinc deficiency in PE. There is increased cortisol production during pregnancy and furthur increase was observed in PE women [29]. Cortisol reduces circulating zinc levels therefore, zinc is expected to be lower in PE. Zinc in plasma is bound to albumin mainly, as serum albumin reduces in pregnancy and along with it, serum zinc also reduces [30]. Zinc levels are reduced in normal pregnancy due to increased cortisol levels but furthur decrease that is seen in PE is due to decrease albumin. Increased intake of iron supplements (upto 65mg/day) may decrease zinc absorption. So, pregnant women taking iron may require zinc supplementation [12]. In addition, placental zinc deficiency also plays a role in the connective

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tissue biosynthesis, maintaining its integrity, which could have an impact on the structure of the spiral arteries[30].

CONCLUSION

It is obvious from this study that modifications of certain micronutrients may play a key role in the pathogenesis of preeclampsia. An increase in iron level and a decrease in zinc levels may be an independent risk marker of preeclampsia before the onset of medical examinations. Careful supplementation with a mixture of antioxidants and micronutrients may be helpful in normalizing the formation of free radicals produced during oxidative stress.

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