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Serum Copper, Zinc and Lipid Peroxidation in Pregnant Women with Preeclampsia in Gorgan

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Abstract: The aim of study was to assay serum copper, zinc and lipid peroxidation levels in pregnant women with and without preeclampsia. There were significant differences between systolic, diastolic blood pressures and copper, Cu/Zn ratio and malondialdehyde among two groups. There were significant differences in weight, pre-pregnancy body mass index, systolic, diastolic blood pressures and copper, Cu/Zn ratio and malondialdehyde levels when compared to healthy pregnant women with mild and severe preeclampsia patients. A positive correlation was observed between systolic and diastolic blood pressure and copper, malondialdehyde and Cu/Zn ratio. Copper and malondialdehyde may play a role in the pathophysiology of preeclampsia.

Keywords: Copper, Zinc, Lipid peroxidation, Preeclampsia

1. INTRODUCTION

Preeclampsia is a disorder that can influence the mother and the fetus during pregnancy. Its symptoms are characterized by high blood pressure, swelling of lower extremities and protein in the urine, sudden weight gain, headaches and changes in vision. High blood pressure and preeclampsia take place in the late second or third trimesters [1, 2]. Preeclampsia complicates 2–8 % of all pregnancies [3]. It has been shown that the incidence of preeclampsia in the developing countries is higher than developed countries [4]. Preeclampsia influences 3.4% of all pregnancies in developing countries. World Health Organization reported that preeclampsia is a major reason of mother and fetus morbidity and mortality [5]. Increased blood pressure is the important sign for the acuteness of preeclampsia. The blood pressure level may be regulated with the use of antihypertensive medicines [6]. Studies on preeclampsia women have revealed that lipid peroxidation levels are increased in blood [7, 8-12] and Placenta [13-15] of these subjects. Some studies have shown elevated reactive oxidative species and placenta oxidative stress were seen during delivery and the period following birth [16] and endothelial dysfunction leading to preeclampsia [17], respectively. Micronutrients deficiencies are usually found in pregnant women [18]. Deficiency of some trace elements may make women susceptible to the development of preeclampsia. Some of these trace elements can regulate the balance between free radicals and antioxidants [19]. Trace elements like copper (Cu) and zinc (Zn) are essential trace elements. These elements may contribute in the development of some diseases like preeclampsia [20].

Copper is an important trace element which takes parts in structure of many enzymes like lysyl oxidase, cytochrome coxidase, tyrosinase, dopamine-β-hydroxylase, peptidylglycine alpha-amidating monooxygenase, monoamine oxidase, ceruloplasmin, and copper–zinc superoxide dismutase. Many different studies have shown that there is an association between occurrence of preeclampsia and trace elements, while some other studies have not shown such association [21]. Copper can produce the highly reactive hydroxyl radical. The generation of this radical can begin lipid peroxidation process which may cause endothelial cell damage [22]. Many studies have shown that copper concentration increased in preeclampsia patients [7].

Alteration of zinc (Zn) may cause pathogenesis of several diseases [23]. Normal homeostasis of Zn is regulated by the actions of Zn transporters like zinc-related protein. These transporters control the level of Zn inside and outside the cell [24, 25]. It has been shown that zinc performs a considerable role for optimal function of more than 300 different enzymes

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[26]. Some studies have indicated that decreased zinc concentrations collaborated with fetal malformations, fetus growth restriction, preterm delivery, preeclampsia, and bleeding after delivery [27, 28]. Serum or placental Zn levels have shown to be low [7, 29] or without change [30, 31] in preeclampsia women. It has been revealed that concentrations of zinc and copper reduced in pre-eclampsia patients [18, 32] while study of Ugwuja *et al*. [33] showed that only copper was statistically different. There are also contradictory studies on the relationship between serum trace element levels and event of preeclampsia [34]. Studies have indicated the possible association of trace elements in fetal growth and evolvement and its relationship to newborn body weight, unhealthiness and rate of death [35]. The aim of this study was to assay serum level of copper and zinc status and lipid peroxidation in pregnant women with and without preeclampsia in Gorgan.

2. MATERIAL AND METHODS

2.1. Study Population

The study was carried out on 100 pregnant women, 50 healthy pregnant women with no complications of any disease and 50 women with preeclampsia in the third trimester were permitted to enter our study in the Sayyad shirazi educational Hospital, Gynecology Department of Golestan University of Medical Sciences, Gorgan, Iran, 2014. The study was approved by Ethical committees of the Research Deputy of University of Medical Sciences. Preeclampsia was defined as a blood pressure higher than 130/85 mmHg and proteinuria with 1+ or greater by dipstick. Severe preeclampsia was distinguished from mild preeclampsia when blood pressure is higher than 160/110 mmHg or proteinuria for mild preeclampsia 1+ - 3+ and for severe preeclampsia greater than 3+ on the dipstick [36].

Diagnosis of preeclampsia was directed by a gynecologist. Special designed questionnaire provided for collection of patient history. Exclusion criteria of subjects were as follow: History of diabetes mellitus, renal, cardiovascular, liver disease, endocrine disorder, any chronic illness. Weight was measured with minimal clothed, using digital scales. Height was measured with tape meter when the shoulder was in a normal position. Calculation of body mass index (BMI) was done by dividing weight in kilograms by height in meters squared [37].

2.2. Blood Sample Preparation

Five milliliter blood samples were taken from the peripheral vein for determination of trace elements and lipid peroxidation (the level of lipid peroxidation expressed as Malondialdehyde (MDA)) after an overnight fast during the third trimester of pregnancy. Blood samples were centrifuged at 3000 rpm for 10 min. The separated serum was used for malondialdehyde (MDA), zinc and copper measurement.

2.3. Analysis

Serum Cu and Zn concentrations were determined by Younglin AAS 8020 atomic absorption spectrophotometer. Malondialdehyde was determined with Kei Satoh method [38].

2.4. Statistical Analysis

The results were expressed in mean ± standard deviation. Statistical analyzation of data was done by SPSS- 16 version software. One way analysis of variance (ANOVA) followed by Post Hoc Tukey's test was utilized to test the differences between groups. Comparison of trace elements and MDA between preeclampsia patient and healthy groups was done using independent sample t test. Correlations between parameters were done by Pearson correlation test. $P < 0.05$ was accepted statistically significant.

3. RESULTS AND DISCUSSION

100 pregnant females were included in this study. The clinical characteristics, trace elements and malondialdehyde of the preeclampsia and healthy pregnant women are indicated in Table **1**. The mean age of preeclampsia patient and healthy groups were 26.50±3.90 and 27.10±4.60 years, respectively. No significant differences were considered in maternal age, height, weight, gestational age and pre-pregnancy body mass index (BMI) among both groups. There were significant differences in systolic and diastolic blood pressures. Serum copper and MDA were significantly increased. No significant decrease was observed in zinc concentration among two groups. In subjects with preeclampsia, Cu/Zn ratio was significantly higher than in healthy pregnant subjects. Serum MDA shows significant increase in preeclampsia patients. Clinical characteristic, trace elements and malondialdehyde of healthy pregnant women and patients with mild and severe preeclampsia are shown in Table **2**. There is significant differences in weight, pre-pregnancy body mass index (BMI), systolic and diastolic blood pressures when healthy pregnant and mild pregnant women were compared with severe preeclampsia patients. There is significant elevation of copper, Cu/Zn ratio and MDA levels when healthy pregnant women with patients with mild and severe preeclampsia are compared. Correlations between serum zinc, copper, MDA and Copper/ Zinc ratio and maternal age, gestational age, pre-pregnant body mass index, systolic and diastolic blood pressure of preeclampsia patients are shown in Table **3**. We observed a significant positive correlation between systolic and diastolic blood pressure and serum copper, MDA and Copper/ Zinc ratio. There were no correlations between other parameters.

Preeclampsia can be associated with an oxidative stress disorder. Imbalance between antioxidant system in the human body and free radicals may cause cell functions and intracellular compartments modifications by oxidative stress [39]. Studies have been shown that there is considerable oxidative stress in normal pregnancies [40]. The exact reason of preeclampsia is not understood. Preeclampsia patients have shown an elevated MDA. The importance of this MDA in the pathogenesis of preeclampsia disease has been indicated [41-43]. Increased serum MDA concentrations in preeclampsia in our study are in agreement with some studies (Table **1**) [7, 8-12]. It has been reported that serum MDA levels were elevated in mild and severe preeclampsia [44] which is in consistence with our results (Table **2**). Many

Table 1. Clinical characteristic, trace elements and malondialdehyde of healthy pregnant women and preeclampsia patients.

Parameters	Healthy pregnant (n=50)	Preeclampsia groups (n=50)	P value
Maternal age(years)	27.10±4.60	26.50±3.90	0.44
Height (m)	1.60±0.09	1.62±0.06	0.23
Weight (Kg)	67.30±10.70	65.70±15.60	0.56
Pre-pregnant body mass index (kg/m2)	26.40±5.0	25.10±6.04	0.23
Gestational age (weeks)	31.50±3.60	30.80±3.30	0.35
Systolic blood pressure (mmHg)	115.20±5.70	148.0±9.6 0	0.0001
Diastolic blood pressure (mmHg)	76.0±6.06	98.60±10.40	0.0001
Copper (mg/L)	1.30±0.34	2.40±0.64	0.0001
Zinc (mg/L)	0.73±0.33	0.71±0.26	0.76
Copper/ Zinc	2.28±1.17	3.85±1.80	0.0001
Malondialdehyde (nμmol/L)	2.95±1.41	4.62±1.17	0.0001

Table 2. Clinical characteristic, trace elements and malondialdehyde of healthy pregnant women and patients with mild and severe preeclampsia.

Parameters	Healthy pregnant group (n=50)	Mild Preeclampsia group (n=35)	Severe Preeclampsia group (n=15)	P value
Maternal age(years)	27.18±4.6	27.0±4.1	25.40±3.5	0.36
Height (m)	1.60±0.09	1.62±0.09	1.61±0.05	0.44
Weight (Kg)	67.32±10.70	62.82±11.90	72.66±21.10	0.049
Pre-pregnant body mass index (kg/m^2)	26.41±5.0	23.82±4.60	28.02±7.90	0.023
Gestational age (weeks)	31.50±3.60	31.08±3.50	30.40±3.10	0.61
Systolic blood pressure (mmHg)	115.20±5.70	142.30±4.20	161.30±3.50	0.0001
Diastolic blood pressure (mmHg)	76.0±6.10	92.85±5.70	112.0±5.60	0.0001
Copper (mg/L)	1.32±0.34	2.26±0.48	2.70±0.85	0.0001
Zinc (mg/L)	0.72±0.04	0.69±0.04	0.78±0.08	0.71
Copper/ Zinc	2.28±0.16	3.73±0.25	4.15±0.61	0.0001
Malondialdehyde (nμmol/ml)	2.96±1.40	4.50±1.20	4.92±0.86	0.0001

studies showed significant elevations in serum MDA levels in both preeclampsia and healthy pregnant women [7, 45-47,]. These findings are not in agreement with our studies and some other studies [7, 48-50]. This study shows that preeclampsia is associated with oxidative stress which is in agreement with the study of other researchers who revealed that oxidative stress increased in preeclampsia [51, 52]. The elevation of serum MDA shows the significance of additional oxidative stress process which occur in preeclampsia patients. Increased level of MDA in preeclampsia women suggest that excessive MDA production may play an important role in the pathophysiology of these patients.

Alteration in level of trace element may play an important role in the development of preeclampsia. Some studies have indicated that there is a significant alteration in serum levels of Cu and Zn in healthy pregnancies [21, 53, 55]. Zn levels inclined to become lower in normal pregnancies [53]. It has been reported that higher concentrations of Cu and lower concentrations of Zn were observed in circulation of preeclampsia patients when compared with healthy pregnant subjects [54, 56]. Studies have shown that zinc concentrations increased in preeclampsia patients when compared with healthy pregnant women [58, 59]. Studies of Diaz *et al*. [30] and Harma *et al*. [59] also showed an increased serum zinc concentration and studies of Adeniyi [60], Ajayi [58], and Borella *et al*. [57] indicated a high plasma zinc concentration. Studies of Mahomed and *et al*. [61] indicated an increase in leukocyte zinc. Adeniyi [60] reported decreased zinc in placental tissue but an increase in plasma zinc concentration. Many studies

Table 3. Parameters correlated with serum zinc, copper, malondialdehyde and Copper/ Zinc ratio of preeclampsia patients.

	Maternal age	Gestational age	Pre-pregnant body mass index	Systolic blood pressure	Diastolic blood pressure
Zinc	R= -0.079 P=0.432	R=-0.055 P=0.588	R== 0.192 P= 0.056	R= 0.031 P= 0.757	R= 0.054 P= 0.595
Copper	R=-0.026 P= 0.801	R= -0.89 P= 0.377	R= 0.107 P=0.289	R= 0.745 P= **0.0001**	R= 0.750 P= **0.0001**
Malondialdehyde	R= -0.029 P= 0.776	R= 0.088 P= 0.383	R= 0.142 P= 0.159	R= 0.613 P= **0.0001**	R= 0.592 P= **0.0001**
Copper/ Zinc	R= 0.004 P= 0.971	R= 0.044 P= 0.667	R= -0.045 P= 0.657	R= 0.429 P= **0.0001**	R= 0.415 P= **0.0001**

R Spearman correlation coefficient

indicated association of trace elements with the etiology of preeclampsia [33, 62]. Studies have been shown that changes in zinc levels are associated with different obstetric diseases [57] and it has admitted that variation in zinc levels cause a harmful effect on fetal growth [31]. Reduction of zinc concentration may depend on decreased levels of zinc binding protein. A study showed that Zn deficiencies in pre-eclampsia indicate no association with hemodilution [63]. Some studies have revealed that plasma copper concentration were high [7, 30], low [18, 33, 61, 64] and unchanged [65] in preeclampsia women. In the present study, serum level of Cu was significantly higher in women with preeclampsia when compared to healthy pregnant women which is not in agreement with other studies (Table **1**) [18, 33, 61, 64, 65]. The possible reasons of copper alterations may be associated with the hormonal, metabolic and enzymatic variations in preeclampsia patients [66]. The increase in copper concentrations in pregnancy is associated with copper carrying protein [24]. There was positive significant correlation between copper, copper /zinc ratio and MDA with systolic and diastolic blood pressure (Table **3**). These parameters may be important factors in early diagnosis of preeclampsia patients and reduction of pathogenesis of this disease in women.

CONCLUSION

This study showed that increased copper, copper /zinc ratio and MDA and positive significant correlation of these factors with systolic and diastolic blood pressure may be related to the development of hypertensive disorders. Preeclampsia is associated with elevated concentrations of copper and MDA production. Increased levels of copper and MDA in preeclampsia women suggest that these factors may play a significant role in the pathophysiology of this disease. Copper can produce the highly reactive hydroxyl radical. The generation of this radical can begin lipid peroxidation process which may cause endothelial cell damage. Increased levels of copper and MDA could be a marker for the risk of preeclampsia before the beginning of medical findings. Supplementation of different antioxidants may be useful to normalize the formation of free radicals produced by increased levels of copper and MDA. This supplementation may be reducing the risk of preeclampsia in women.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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