Biol Trace Elem Res (2013) 154:14–20
DOI 10.1007/s12011-013-9721-9

Comparative Study of Serum Zinc, Copper, Manganese, and Iron in Preeclamptic Pregnant Women

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Received: 6 April 2013 / Accepted: 29 May 2013 / Published online: 9 June 2013

Abstract Preeclampsia complicates 2–8 % of all pregnancies and it is one of the leading causes of maternal mortality and pre-term delivery in the world. Unfortunately, there is scarcity of document discussing the circulating level of several essential trace elements in preeclampsia patients in Bangladesh. The present study was designed to evaluate the serum concentration of four trace elements, namely zinc, copper, manganese, and iron, in preeclamptic pregnant women. The study was conducted as a case–control study with 50 preeclamptic pregnant women as cases and 58 normotensive pregnant women as controls. Obstetric, anthropometric, and clinical data were collected at routine obstetric visits. Serum trace elements were determined by flame atomic absorption spectroscopy. Independent sample *t* test and Pearson's correlation test were done for the statistical analysis using the statistical software package SPSS, version 16.0 (SPSS Inc., Chicago, IL). We observed significant differences for gestational age, body mass index, and systolic and diastolic blood pressure between patient and control groups ($p<0.05$). Analysis of serum trace elements explored significantly lower level of all the four elements in preeclampsia patients in comparison to the control group ($p<0.05$). Pearson's correlation analysis explored that the correlation between serum level of different trace elements was statistically insignificant ($p>0.05$) except the correlation between zinc and iron in preeclampsia patients ($p<0.05$). Establishment of inter-element relationship strongly supports that there was a disturbance in the element homeostasis in patient with preeclampsia. In conclusion, our study suggests that preeclampsia patients have considerably lower level of serum zinc, copper, manganese, and iron compared to the healthy pregnant women.

Keywords Preeclampsia · Pregnant women · Hypertension · Trace elements · Inter-element relationship

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Introduction

Preeclampsia (PE), also known as toxemia or pregnancy-induced hypertension is a human pregnancy-specific disorder which can be defined as the new onset of hypertension and significant proteinuria in a previously normotensive women on or after the 20th week of gestation with or without pathological edema [1, 2]. Hypertension in preeclampsia is characterized by a systolic blood pressure of ≥140 mmHg and diastolic pressure of ≥90 mmHg, at least on two measurements within 6 h or more [3, 4]. This disorder complicates 2–8 % of all pregnancies and it is one of the leading causes of maternal mortality and preterm delivery throughout the world [5]. However, the incidence of preeclampsia has fallen in developed countries due to the improved antenatal care, but its incidence is still high in the developing countries [6]. Preeclampsia and eclampsia cause about 16 % of maternal deaths in Bangladesh [7]. Abortion or delivery is the only cure for preeclampsia. The obstetrician must focus on minimizing maternal risk while maximizing fetal maturity. As elevated level of blood pressure is the major indicator for the severity of preeclampsia and its complications, antihypertensive medicines may be used to regulate the blood pressure and to prevent such complications. Magnesium sulfate can be used to stabilize convulsion disorder of preeclampsia [8].

Nutritional deficiencies are commonly found in pregnant women and it is well established that the pregnant women from developing countries usually consume diets that are low in minerals and vitamins [9]. Deficiency of several essential micronutrients may be a predisposing factor in the development of preeclampsia because nutrient can modulate oxidative stress by increasing or decreasing free radicals or antioxidants and/or by providing substrate for the formation of free radicals [10, 11].

Trace elements are crucial for maintaining human health, as well as for preventing several health problems. Alteration of normal homeostasis of trace elements may adversely affect biological processes leading to many diseases processes [12]. Zinc (Zn) acts as an intracellular signaling molecule which is able to communicate between cells by converting extracellular stimuli to intracellular signals and controlling intracellular actions. Thus, alteration of Zn homeostasis and dysfunction in the signaling function of Zn may cause pathogenesis of several diseases [13, 14]. Normal homeostasis of Zn is regulated by the harmonized actions of Zn transporters such as zinc- and iron-related protein (Zip) which controls Zn influx and efflux and thus controls the concentration of Zn inside and outside the cell [15, 16]. Zn also plays a substantial role in enhancing reproductive health and it is also required for optimal cellular function working with more than 300 different enzymes [17, 18]. Evidences suggest that lower levels of plasma Zn are associated with detrimental pregnancy outcomes such as fetal malformations, fetus growth restriction, preterm delivery, preeclampsia, and bleeding after delivery [19, 20]. Copper (Cu) is another important trace element which connects with many Cu-dependent enzymes such as lysyl oxidase, cytochrome coxidase, tyrosinase, dopamine-β-hydroxylase, peptidylglycine alpha-amidating monooxygenase, monoamine oxidase, ceruloplasmin, and copper–zinc superoxide dismutase (Cu-Zn SOD) and all these enzymes act as antioxidant defense system. The normal homeostasis of these enzymes is necessary for human beings.

Manganese (Mn) is a mineral that helps to form bone and cartilage. It also plays a vital role as a cofactor for a variety of enzymes involved in amino acid, lipid, and carbohydrate metabolism and immune function and connective tissue growth [21]. Mn acts as a potential antioxidant because it is a part of manganese superoxide dismutase (Mn-SOD) which helps to protect cells from damage. Besides its potential biological activity, overexposure may cause neurotoxic effect known as “manganism” which is characterized by behavioral disturbances [21, 22]. Some Zip transporters of Zn including ZIP8 and ZIP14 mobilize Mn across biological membranes and Mn homeostasis is thus regulated by these Zn transporters [23, 24]. Recent evidence suggests that deficiency of Zn may affect the Mn concentration which subsequently may cause metabolic disorder and growth retardation [16]. Iron (Fe) requirement is increased in pregnancy (approximately 840 mg), especially in the third trimester, which may be several times higher than other stages of the life cycle [25]. Deficiency of iron in pregnant women may restrict oxygen supply to cell resulting in weakness, reduced work performance, and disturbed immunity. Decreased level of iron can also lead to anemia in the early stage of pregnancy which can double or even triple the possibility of premature delivery or low birth weight baby [26]. Some researchers identified that depleted level of these trace elements acts as a contributing factor to the pathophysiological event of preeclampsia while other found no such association between preeclampsia and trace elements [27]. Due to these facts, we investigate the level of trace elements in preeclamptic pregnant women and thereby find out the exact role of these elements in the pathogenesis of preeclampsia.

Materials

The reagents used for the study were of analytical grade from commercially available company. Standards of Zn, Cu, Fe, and Mn were sourced from Buck Scientific, USA. Hydrochloric acid (37 %) and nitric acid were purchased from Merck, Germany.

Methods

Study Design and Data Collection

This case–control study was carried out in the Department of Obstetrics and Gynecology, Noakhali Medical College Hospital, Bangladesh, from June 2012 to February 2013. Ethical permission was taken from the ethical committee of the respective hospital. For the study purpose, 50 diagnosed cases of preeclampsia with gestational period >20 weeks were recruited, and for comparison, 58 normotensive pregnant women were selected as control subjects who matched their gestational period with the cases. Diagnosis of preeclampsia was conducted by a specialized obstetrician and gynecologist. Detailed patient history was taken with a well-designed questionnaire. Each and every patient was briefed about the purpose of this study prior to data collection. Initially, a pilot study was carried out with small number of patients using a predesigned questionnaire to set the variables of the study. Then, necessary modification was done in the questionnaire as per as the objective of the study before conducting the final study. Subjects with history of diabetes mellitus, renal, cardiovascular, liver disease, endocrine disorder, any chronic illness were excluded from the study. Patients who were not sufficiently cooperative to share their clinical data and denied to donate blood sample were also excluded.

Blood Sample Collection

Five-milliliter venous blood samples were drawn from each patient in a metal-free sterile tube after 8 h fasting condition. The blood sample was then kept at room temperature for about 30 min to clot and centrifuged at 3,000 rpm for 15 min to extract the serum. The serum was taken in an Eppendorf tube and stored at −80 °C until the study day.

Analytical Procedure

Determination of trace element was conducted by flame atomic absorption spectrometry (Varian SpectraAA 220) as well as graphite furnace following the method of Czuprynet al. [28]. The samples were diluted with deionized water by a dilution factor of 10. Different concentrations (0.5, 1.0, 2.0, 5.0, and 10.0 mg/L) of trace elements were used for calibration of standard graphs. Absorbances were taken at 213.9, 224.8, 279.8, and 248.3 nm for zinc, copper, manganese, and iron, respectively, in the atomic absorption spectrometer. To verify the assay accuracy and to maintain quality, the standard solutions were run for every ten-test sample. A software package (SpectrAA Software) was used to calculate the concentration of zinc, copper, manganese, and iron.

Data Analysis

All data were expressed as mean ± standard error mean (mean ± SEM) with their corresponding *p* values. Statistical analysis was performed using the statistical software package SPSS, version 16.0 (SPSS Inc., Chicago, IL). Comparison of trace elements between patient and control groups was performed using independent sample *t* test. Pearson's correlation analysis was used to find the correlation among the various study parameters.

Results and Discussion

Results

Characteristics of Subjects

This study comprised of 50 preeclamptic pregnant women as cases and 58 normal healthy pregnant women as controls. Obstetric, anthropometric, and clinical features of the cases and controls are presented in Table 1. It was observed that the mean maternal age of the patients and controls was 25.46±0.85 and 25.76±0.73 years, respectively, whereas the mean gestational age at diagnosis was 35.32±0.37 and 36.79±0.27 weeks, respectively. The mean values of body mass index (BMI), Hb, and creatinine were 25.30±0.36 kg/m^2, 10.96±0.15 %, and 0.96±0.02 mg/dL for PE group and 23.48±0.28 kg/m^2, 10.98±0.13 %, and 0.94±0.02 mg/dL for the healthy control group. The values of systolic and diastolic blood pressure (SBP and DBP, respectively) were 167.8±2.54 and 108.2±1.86 mmHg for the patient group and 120.34±1.16 and 79.66±0.96 mmHg for control group. Statistical analysis of these parameters showed that the differences of gestational age, BMI, SBP, and DBP were significant ($p<0.05$) between patient and control groups, but no such differences were observed for maternal age, Hb, and creatinine between the two groups ($p>0.05$).

Element Concentration

Analysis of serum trace elements found that the mean values of Zn, Cu, Fe, and Mn were 0.77±0.05, 1.98±0.10, 1.13±0.22, and 0.08±0.02 mg/L for the patient group and 0.98±0.03, 2.58±0.06, 1.96±0.32, and 0.14±0.02 mg/L for the control group, respectively (Table 2). There was significant difference for all the elements between the patients and controls ($p<0.05$). The data were further analyzed in order to determine the effect of maternal age, gestational age, BMI, SBP, and DBP on the serum trace element level in preeclampsia patients (Table 3). We observed a significant positive correlation between maternal age and Fe ($r=0.300$, $p=0.035$); BMI and Mn ($r=0.310$, $p=0.028$); and SBP and Cu ($r=0.279$, $p=0.050$) in PE patients.

Inter-Element Correlations

The present study establishes inter-element correlations for the analyzed elements between patient and control subjects which exhibited a positive (direct) or negative (inverse) correlations for selected elements. The correlation coefficient and the statistical confidence levels at which the correlations were determined are presented in Table 4. All these correlations were statistically insignificant ($p>0.05$) except the correlation between Zn and Fe in preeclampsia patients ($p<0.05$).

Discussion

Preeclampsia is a life-threatening complication during pregnancy which may threaten the life of both mother and fetus. We conducted this study on the basis of hypothesis that decreased concentration of trace element may play a major role in the development of preeclampsia. In our study, we observed no significant difference for maternal age between

Table 1 Obstetric, anthropometric, and clinical characteristics of the study population

Parameters	Patient group	Control group	p value
Maternal age (years)	25.46±0.85	25.76±0.73	0.778, NS
Gestational age (weeks)	35.32±0.37	36.79±0.27	0.001*
BMI (kg/m^2)	25.30±0.36	23.48±0.28	0.041*
SBP (mmHg)	167.8±2.54	120.34±1.16	0.000*
DBP (mmHg)	108.2±1.86	79.66±0.96	0.000*
Hb (%)	10.96±0.15	10.98±0.13	0.891, NS
Creatinine (mg/dL)	0.96±0.02	0.94±0.02	0.431, NS

All values are expressed in mean ± SEM

NS not significant

* $p<0.05$ (significant difference between patient and control groups at 95 % confidence interval)

the patients and control groups ($p>0.05$) which confirms previously conducted study [29, 30]. But the gestational age was significantly lower in preeclampsia group than the control group ($p<0.05$). This is an agreement with previous reports [1, 30]. The complications of preeclampsia start on or after 20 weeks of gestation and its complications become more severe after 28 weeks. Delivery is the only effective treatment of the disease; thus, preterm delivery of the baby to save the life of mother may be a cause of lower gestational age in preeclampsia patients because these patients attended relatively early period of their gestation for antenatal care. High maternal BMI is associated with large number of pregnancy-related complications such as preeclampsia, eclampsia, pre-term and post-term delivery, and postpartum hemorrhage. Several studies reported that obese women are at increased risk for developing preeclampsia and women with greater BMI in pregnancy are more likely to become hypertensive than those with lower BMI [31, 32]. We also observed a significant difference for BMI among the preeclamptic pregnant and normal pregnant women. The mechanism by which obesity may cause preeclampsia is illusive. However, it is suggested that obesity has a strong correlation with insulin resistance and contributes to type II diabetes and gestational diabetes, both of which are associated with a higher risk of cardiovascular diseases, and thus play an enormous role in the development of preeclampsia.

Table 2 Serum levels of Cu, Zn, Mn, and Fe in the study population

Parameters	Patient group	Control group	p value
Zn (mg/L)	0.77±0.05	0.98±0.03	0.000*
Cu (mg/L)	1.98±0.10	2.58±0.06	0.000*
Mn (mg/L)	0.08±0.02	0.14±0.02	0.032*
Fe (mg/L)	1.13±0.22	1.96±0.32	0.039*

All values are expressed in mean ± SEM

* $p<0.05$ (significant difference between patient and control groups at 95 % confidence interval)

In this study, systolic and diastolic blood pressures were normal in the control group, but both were very high in the preeclampsia group. That is one of the symptoms of preeclampsia and there was a significant difference for both systolic and diastolic blood pressures between the patient and control groups ($p<0.05$). This confirms an earlier investigation by Genc et al. [1] who reported a systolic blood pressure of 154 mmHg and a diastolic blood pressure of 99.04 mmHg. The little difference between Genc et al. [1] result and ours may be due to ethnic differences. In our study, we observed that both preeclamptic and normal pregnant women had lower level of Hb and no significant difference was observed between the patient and control groups which comply with previous studies [33]. Although majority of available studies generally observed a significant elevation of creatinine levels in preeclampsia [34, 35], opposite result was also found [36, 37]. In this study, it was observed that the level of serum creatinine was almost same in both patient and control groups, i.e., no significant difference was found between the two groups ($p>0.05$).

Trace elements are present in metalloprotein (zinc), ceruloplasmin (copper), superoxide dismutase (copper, zinc, and manganese), and hemoglobin (iron) providing

Table 3 Effect of maternal age, gestational age, BMI, SBP, and DBP on serum trace elements of preeclampsia patients

Parameters		Zn	Cu	Mn	Fe
Maternal age (year)	R	0.272	0.106	−0.027	0.300*
	p	0.056	0.464	0.853	0.035
Gestational age (week)	R	−0.110	0.043	0.054	−0.042
	p	0.447	0.767	0.712	0.772
BMI (kg/m$^{2)}$	R	0.038	0.147	0.310*	0.158
	p	0.791	0.307	0.028	0.272
SBP (mm Hg)	R	0.012	0.279*	0.150	0.006
	p	0.936	0.050	0.298	0.968
DBP (mm Hg)	R	0.023	0.235	0.129	0.135
	p	0.876	0.101	0.372	0.350

Values with a negative sign indicate an inverse correlation

* $p<0.05$ (Correlation is significant at 0.05 level (two tailed))

Table 4 Comparison of inter-element relationships between the patient and control groups

Correlation parameters	Correlation coefficient (*R*)	
	Patient group	Control group
Zn and Cu	0.152	0.024
Zn and Mn	−0.190	−0.074
Zn and Fe	0.427[a]	0.045
Cu and Mn	0.036	0.027
Cu and Fe	0.074	0.138
Mn and Fe	−0.084	0.058

Values with a negative sign indicate an inverse correlation

[a] Correlation is significant at 0.01 level (two tailed)

the fact that deficiency or decreased concentration may be a predisposing factor in the development of preeclampsia. From the findings of the present study, it was observed that there was a significant decrease in the concentration of all the trace elements when compared to the control group ($p<0.05$). Although these findings provide a role of zinc, copper, manganese, and iron in the development and pathogenesis of preeclampsia, this result must be interpreted with caution as we did not investigate the dietary intake of preeclamptic women to find out whether the reduced levels of trace elements arise from nutritional deficiencies or not. The relatively lower level of trace elements in preeclamptic pregnant women compared with healthy pregnant women may also result from hemodilution due to fluid retention in these patients.

Zinc is a structural component of several proteins such as growth factors, cytokines, receptors, enzymes, and transcription which play an important role in the cellular signaling pathways. Approximately 10 % of all protein in human body binds with Zn and the biological activity of these Zn bound protein depends on the concentration of Zn in the body [13]. On the other hand, neuroscientists identified the physiological role of Zn not only as a micronutrient and a component of proteins, but also as an ionic signal. A recent study suggests that Zn^{2+} acts as a signaling molecule called Zn signal that controls various intracellular signaling pathways such as growth factor-mediated and antigen receptor-mediated pathways [38]. In addition, Zn deficiency has a negative effect on Cu-Zn SOD enzyme system [39]. Subsequently impaired Cu-Zn SOD activity contributes to the oxidative damage in the body which may worsen several disease states [40]. This study showed a significant decrease in the serum zinc concentration of preeclampsia patients compared to the controls which supports the report of other studies [41, 42].

Copper is another essential trace element which is involved in the function of several cuproenzymes and it connects with Cu-Zn SOD which is a potential antioxidant defense enzyme. Thus, as a part of powerful antioxidant, it helps to protect the cell from damage. It is also present in ceruloplasmin which catalyzes the conversion of ferric ion to its ferrous form and promotes the absorption of iron from the gastrointestinal tract [43]. Our result reported significantly lower level of copper in preeclamptic patients when compared to control subjects ($p<0.05$). This result is consistent with previously conducted studies [9, 44]. Although the copper level found in this study was relatively higher, it still matches with other study [45].

Manganese acts as a cofactor for a large number of enzymatic systems including transferases, oxidoreductases, hydrolases, lyases, isomerases, ligases, and lectins and, most importantly, it is a component of Mn-SOD which deals with the toxic effect of superoxide, formed from the electron reduction of dioxygen [46]. Several studies reported that low level of manganese in serum may cause accumulation of superoxides which could consequently trigger preeclampsia and its complications [47, 48]. Thus, significant depletion of serum level of manganese ($p<0.05$) as reported in the current study may trigger the pathogenesis of preeclampsia.

Iron is the most essential trace element which plays an important role for the synthesis of hemoglobin and also needed for additional erythrocyte production during pregnancy. Some report suggests that about 750–800 mg of elemental iron is necessary during the time period of pregnancy [49]. Although our study found significantly lower level of iron in the preeclamptic pregnant group in comparison to the control group ($p<0.05$), previous studies produced inconsistent results regarding the serum concentration of iron on the pathophysiology of preeclampsia. Ugwuja et al. [44] and Rathore et al. [49] found significantly lower level of iron in preeclampsia while Balla et al. [50] and Hubel et al. [51] identified high level of iron as a contributing factor for the development of preeclampsia. Thus, we recommend further research to explain the exact role of iron in the pathogenesis of preeclampsia.

Conclusion

Our study explored that preeclamptic pregnant women have low serum concentration of Zn, Cu, Mn and Fe than the healthy pregnant women which suggests the possible involvement of depleted serum trace element in the pathogenesis of preeclampsia. We thus recommend dietary supplementation to reduce the risk of preeclampsia which may require further study.

Acknowledgments The authors are thankful to all the staffs, nurses, and physicians of the Department of Obstetrics and Gynecology, Noakhali Medical College Hospital, Bangladesh for their technical and administrative support. The authors are also thankful to all the participants of this study.

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