Changes in Copper, Zinc, and Malondialdehyde Levels and Superoxide Dismutase Activities in Pre-Eclamptic Pregnancies

Authors' Contribution:
Study Design **A**
Data Collection **B**
Statistical Analysis **C**
Data Interpretation **D**
Manuscript Preparation **E**
Literature Search **F**
Funds Collection **G**

ACE 1 **Murat Bakacak**
BD 2 **Metin Kılınç**
BC 1 **Salih Serin**
DF 1 **Önder Ercan**
AD 1 **Bülent Köstü**
BC 1 **Fazıl Avcı**
BC 1 **Hakan Kıran**
AE 1 **Gürkan Kıran**

1 Department of Obstetrics and Gynecology, Kahramanmaras Sutcu Imam University, School of Medicine, Kahramanmaraş, Turkey
2 Department of Biochemistry, Kahramanmaras Sutcu Imam University, School of Medicine, Kahramanmaraş, Turkey

Corresponding Author: Murat Bakacak, e-mail: muratbakacak46@gmail.com
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Background: Preeclampsia (PE) is a hypertensive disorder that occurs in 2% to 8% of pregnancies. Although numerous studies have investigated the etiology and pathophysiology of preeclampsia, the precise pathological mechanisms remain poorly understood. Hence, in the present study malondialdehyde (MDA) levels and SOD expression, and Cu and Zn concentrations and ratios were correlated with birth weights in pregnant women with and without PE, and in non-pregnant females of reproductive age.

Material/Methods: Malondialdehyde (MDA) levels and superoxide dismutase (SOD) activities were determined spectrophotometrically, and Cu and Zn levels were determined using atomic absorption spectrometry in serum from 42 non-pregnant women (NP), 40 healthy pregnant women (HP), and 38 pre-eclamptic pregnant (PE) women. Subsequently, Cu/Zn ratios were calculated and associations with birth weights were analyzed using Spearman correlations.

Results: Cu, Zn, and MDA levels and Cu/Zn ratios were significantly higher in the PE group than in the HP and NP groups, and were significantly higher in the HP than in the NP group ($p<0.001$ and $p<0.001$; respectively). In contrast, serum Zn and SOD levels were significantly lower in the PE group than in HP and NP groups, and were significantly lower in the HP group than in the NP group ($p<0.001$ and $p<0.001$; respectively). However, only Cu and Zn levels were significantly associated with fetal birth weights ($r=-0.433$, $p<0.001$).

Conclusions: Serum Cu/Zn ratios may reflect vascular complications of PE, and the ensuing increases in lipid peroxidation may play important pathogenic roles.

MeSH Keywords: **Antioxidants • Copper • Lipid Peroxidation • Pre-Eclampsia • Zinc**

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Background

Pre-eclampsia (PE) is a hypertensive disorder of pregnancy that occurs in 2% to 8% of pregnancies, and is a major cause of maternal and fetal morbidity and mortality [1,2]. Increased lipid peroxidation reportedly plays an important role in the etiology of PE by inducing endothelial dysfunction. In particular, the lipid peroxide (LPO) malondialdehyde (MDA) has been associated with decreased perfusion in placental tissue, presumably reflecting a free radical process [3,4]. Moreover, imbalances of LPOs and antioxidants have been associated with endothelial damage in multiple studies [5,6].

Oxidative imbalances and decreased anti-oxidant activities have been identified as major etiological factors in pre-eclamptic women. Superoxide dismutase (SOD) is a well-characterized antioxidant enzyme that prevents free radical mediated injury *in vivo* and *in vitro* by metabolizing superoxide anions that are known to damage human tissues [7,8]. In addition, copper (Cu) and zinc (Zn) are known to play multiple biochemical roles as catalysts and enzyme and hormone cofactors, particularly in antioxidant enzymes such as SOD [9]. It is well known that variations in concentrations and homeostasis of these micronutrients in the body contribute to the pathophysiology of various disorders and diseases [9]. Moreover, as a transition metal, Cu has the highest pro-oxidant capacity of biological ions, and Cu and Zn are both obligate cofactors of first-step antioxidant enzymes [10].

Oxidative stress and systemic inflammatory responses are strongly elevated in pre-eclampsia [11] and evidence of placental oxidative stress in cases of early onset preeclampsia is conclusive, with increased concentrations of protein carbonyls, lipid peroxides, nitrotyrosine residues, and DNA oxidation [12]. Because early onset pre-eclampsia is associated with deficiencies in the conversion of spiral arteries, the origins of the ensuing oxidative stress are thought to be vascular [13]. In agreement, myometrial arterial segments are adversely affected in preeclampsia, and imbalances of LPO products such as MDA and antioxidants likely lead to endothelial damage. In addition, poorly perfused placental tissue may facilitate the production of free radicals that cause general lipid peroxidation [11]. Free radical production is relatively low in normal endothelial cells, reflecting the presence of active defence systems that comprise chemical scavengers, antioxidant molecules, and antioxidant enzymes such as SOD [10]. Accordingly, in the classic two-stage model of pre-eclampsia, oxidative stress in the placenta may lead to release and maternal circulation of factors that stimulate inflammatory responses and activate maternal endothelial cells [13].

Multiple studies have associated changes in serum Cu and Zn levels with hypertensive disorders in pregnancy [14–17] and in other diseases, and instability of Cu/Zn ratios are reportedly a more reliable indicator of vascular complications and diseases than Zn or Cu status alone [13]. Thus, in the present study, we Determined MDA levels, SOD activities, and Cu and Zn concentrations, and calculated Cu/Zn ratios in pregnant females with and without hypertensive disorders and in non-pregnant females of reproductive age. Subsequently, correlations between these parameters and fetal birth weights were investigated.

Material and Methods

Study subjects were recruited at the Obstetrics and Gynecology Department, Kahramanmaras Sutcu Imam University Hospital. The study included 120 females (42 non-pregnant, 40 healthy pregnant, and 38 pre-eclamptic pregnant). Preeclamptic patients were referred to our clinic with initial diagnoses of PE at 32–38 gestational weeks or were diagnosed with PE during routine antenatal visits. Only pre-eclamptic females with normal blood pressure during the first 20 gestational weeks, no history of twin pregnancy, recurrent miscarriage, fetal growth retardation, metabolic disorders, abruptio placenta, thrombophilia, renal disease, chronic hypertension, or diabetes mellitus, and no history of antioxidant or antihypertensive medication were recruited. Pregnant patients who were hospitalized with other disorders in the same period and visited the hospital for regular clinical checkups were recruited into the healthy pregnant group. Subjects of the non-pregnant group were recruited at routine gynecological visits.

Pre-eclampsia was defined according to the criteria of the "Report of the American College of Obstetricians and Gynecologists Task Force on Hypertension in Pregnancy", as systolic blood pressure (BP) of ≥140 mmHg and/or diastolic BP of ≥90 mmHg BP in two measurements taken at least 4 h apart, and proteinuria of ≥300 mg protein/24 h [18]. Gestational age was defined as the interval between the first day of the mother's last menstrual period. When the last menstrual date was unknown, gestational age was calculated using ultrasonographic examinations during the first trimester. None of the study subjects were taking drugs at the time of blood sampling and all gave written informed consent. Demographic and clinical data were collected during routine obstetric visits. Subjects of the healthy pregnant group had no medical conditions, such as diabetes or obesity, and no history of "small for gestational age" babies or hypertensive disorders in any previous pregnancy.

Maternal and infant medical records were reviewed for details of antepartum labor, delivery characteristics, birth weights, and gestational ages of newborns at delivery. Patients were immediately hospitalized at the time of initial diagnosis if 12-hour

fasting was appropriate, or the next morning after at least 12-hour fasting. Subsequently, venous blood samples were taken from the forearm veins of fasted patients and were placed in additive and no-additive Vacutainer (Becton-Dickinson, Franklin Lakes, NJ) blood-collecting tubes in accordance with standard hospital procedures for venipuncture and sample collection. After clot formation, no-additive blood samples were centrifuged for 10 minutes at 3000 g and serum and plasma were stored separately at –70°C until analysis. Approval for the study was granted by the Local Research Ethics Committee of Kahramanmaraş Sütçü İmam University School of Medicine.

Determination of serum MDA levels

Plasma lipid peroxidation was assessed according to MDA concentrations, which were measured using the methods described by Ohkawa et al. [19]. Briefly, MDA concentrations were determined by spectrophotometric quantitation of the secondary MDA product after lipid peroxidation by thiobarbituric acid (TBA). Specimens were incubated with TBA under aerobic conditions (pH 3 and 4) at 90–95°C, and absorbance was determined at 532 nm.

Hemoglobin levels were spectrophotometrically determined using the cyanomethemoglobin method with Drabkin's solution at 520 nm. All spectrophotometric measurements were taken using a Shimadzu-UV120 spectrophotometer (Shimadzu, Japan).

Determination of serum SOD activity

SOD activity was measured using the method described by Fridovich [20] based on the assumption that SOD accelerates the dismutation of toxic superoxide radicals to H_2O_2 and molecular oxygen. Briefly, superoxide radicals were generated using a xanthine and xanthine oxidase system in the presence and absence of serum samples, and after reaction with p-iodonitrotetrazolium violet, absorbance of the resulting red formazan dye was determined at 505 nm. SOD activity was expressed as U/g hemoglobin.

Determination of serum Cu levels

Serum Cu levels were measured using an atomic absorption spectrophotometer flame photometer (Analyst 800, Perkin Elmer, Inc., USA). All samples and standards were diluted (rate of 1/2) with 10% glycerol, and serum Cu concentrations (µg/dl) were calculated using a commercial Cu standard (1000 mg/L) curve [21].

Determination of serum Zn levels

Serum Zn levels were measured using an atomic absorption spectrophotometer flame photometer (Analyst 800, Perkin Elmer, Inc., USA). All samples and standards were diluted (rate of 1/4) with 5% glycerol, and serum Zn concentrations (µg/dl) were calculated using a commercial Zn standard (1000 mg/L) curve [21].

Statistical analysis

Statistical analyses were performed using SPSS 22.0 (IBM statistics for Windows version 22, IBM Corporation, Armonk, New York, USA) software. Distribution normality of data was assessed using the Shapiro–Wilk test, and variability coefficients were calculated. Normally and non-normally distributed data were analyzed using parametric and nonparametric methods, respectively. Pairwise independent group comparisons were made using the Mann-Whitney U test, and multiple comparisons were made using one-way ANOVA (Robust Test: Brown-Forsythe) and Kruskal-Wallis H tests. Post Hoc analyses were performed using non-parametric post-hoc tests (Miller 1966) and Games-Howell tests. Correlations between variables were identified using Spearman's rho test. Quantitative data are presented as means ±SD (standard deviation) and median ranges (maximum–minimum) and categorical data are presented as numbers (n) and percentages (%). Differences and correlations were considered significant when $p < 0.05$.

Results

Demographic and clinical parameters of 42 subjects in the NP group, 40 in the HP group, and 38 in the PE group are presented in Table 1. Although no significant difference were observed between NP and HP groups, systolic and diastolic blood pressure values were higher in the PE group than in NP and HP groups ($p < 0.001$). Moreover, weeks of gestation and fetal birth weights were significantly lower in the PE group than in the HP group ($p < 0.001$ and $p < 0.001$, respectively).

Serum Cu, Zn, and MDA levels, SOD activities, and Cu/Zn ratios are presented in Table 2. Cu and MDA levels and Cu/Zn ratios were significantly higher in the PE group than in the HP and NP groups, and were higher in the HP group than in the NP group ($p < 0.001$ and $p < 0.001$, respectively). Serum Zn levels and SOD activities were significantly lower in the PE group than in the HP and NP groups, and were lower in the HP group than in the NP group ($p < 0.001$ and $p < 0.001$, respectively).

In analyses of serum Cu, Zn, MDA concentrations, SOD activities, Cu/Zn ratios and fetal birth weights (Table 3), no significant correlations were identified in the HP group. However, increased Cu/Zn ratios and fetal birth weights were significant negatively correlated in the PE group (r=-0.433, $p < 0.001$).

Table 1. Demographic features and clinical parameters.

	Non pregnant (n=42)		Healthy pregnant (n=40)		Pre-eclampsia (n=38)		P Value
Age (years)*	28.2±3.61		28.7±3.82		29.2±3.56		NS
Systolic blood pressure (mmHg)**	120	(140–100)	120	(135–100)	170	(180–155)[a,b]	<0.001
Diastolic blood pressure (mmHg)**	75	(85–45)	72.5	(85–50)	105	(120–90)[a,b]	<0.001
Fetal birthweight (g)**	–		3220	(3810–2010)	2430	(3120–2010)	<0.001
Gestation at blood sampling (weeks)**	–		36	(38–35)	35	(38–32)	0.004
Gestation at delivery (weeks)**	–		38	(42–36)	36	(39–32)	<0.001
Gravidity**	–		2	(5–1)	2	(5–1)	NS
Parity**	–		1	(4–0)	1	(4–0)	NS

OneWay ANOVA (Brown-Forsythe) – Kruskal-Wallis Test Post Hoc Test: non-parametric posthoc test (Miller(1966) – Mann-Whitney U Test. * Mean ±SD (standard deviation); ** Median Range (Maximum–Minimum); [a] P<0.001 significant compared to the Non pregnant group; [b] P<0.001 significant compared to the Healthy pregnant group.

Table 2. Mean serum Cu, Zn, MDA, and SOD levels and Cu/Zn ratios of study groups.

	Non pregnant (n=42)		Healthy pregnant (n=40)		Pre-eclampsia (n=38)		P Value
Cu (μg/dl) **	98.27	(156.3–76.7)	152.45	(187.32–104.56)[a]	199.5	(281.86–114.4)[a,b]	<0.001
Zn (μg/dl)**	119.38	(145.21–101.9)	108.45	(138.55–88.12)	81.24	(110.65–62.4)[a,b]	<0.001
Cu/Zn *	0.9±0.16		1.4±0.21[a]		2.4±0.60[a,b]		<0.001
MDA (nmol/ml) **	8.7	(16–4.6)	15.6	(25.4–7.5)[a]	26.8	(36.4–16.5)[a,b]	<0.001
SOD (U/ml) **	36.86	(52.4–30.4)	27.38	(45.76–19.3)[a]	18.82	(25.77–10.31)[a,b]	<0.001

OneWay ANOVA (Brown-Forsythe) – Kruskal-Wallis Test Post Hoc Test: non-parametric posthoc test (Miller(1966) * Mean ±SD (standard deviation); ** Median Range (Maximum–Minimum); [a] P<0.001 significant compared to the Non pregnant group; [b] P<0.001 significant compared to the Healthy pregnant group.

Table 3. Correlations between fetal birth weights and serum Cu, Zn, MDA, and SOD levels, and Cu/Zn ratios.

		Healthy pregnant		Pre-eclampsia	
		r	P Value	r	P Value
Fetal birth weight	Cu	0.196	NS	−0.198	NS
	Zn	0.125	NS	0.220	NS
	Cu/Zn	0.209	NS	−0.433	<0.001
	MDA	0.043	NS	−0.122	NS
	SOD	−0.093	NS	−0.152	NS

Spearman's rho Test; r: Correlation Coefficient.

Discussion

Although the causes of pre-eclampsia are not fully understood, associations with oxidative stress disorders have been demonstrated, and oxidative stress is known to reflect imbalances of antioxidant systems and free radical concentrations that lead to changes in cell function [22]. Increased serum MDA concentrations in pre-eclamptic women have been

shown in previous studies [9,22]. In agreement, the present data show that MDA levels were increased and SOD activities were decreased in healthy pregnant women compared with non-pregnant females, and in pre-eclamptic pregnant females compared with healthy pregnant and non-pregnant women. Moreover, significantly elevated serum MDA levels have been demonstrated in both pre-eclamptic and healthy pregnancies [8,17], and significant differences have been shown between pre-eclamptic pregnant women and non-pregnant and healthy pregnant women, and between pregnant and non-pregnant women [8,17]. In a similar previous study, the activity of the antioxidant enzyme SOD was significantly reduced in pre-eclamptic and eclamptic cases [23,24], indicating that inappropriate or excessive lipid peroxidation may play an important role in the pathophysiology of pre-eclampsia. In addition, the present data indicate that increased MDA and decreased SOD levels are consequences of pre-eclamptic and normal pregnancies, and may directly reflect hypertension.

Lipid peroxides, anti-oxidants, and nitric oxide are considered central to the etiology of essential hypertension [25]. Moreover, increased Cu and MDA levels, decreased glutathione, and Zn levels, and decreased SOD activity were observed in obese non-diabetic children and adolescents, potentially disposing these individuals to hypertension [26]. Previous data demonstrate a direct cause-and-effect correlation between oxidative stress and altered amyloid-β production, suggesting a molecular mechanism by which naturally occurring lipid peroxidation products contribute to the generation of toxic amyloid-β_{42} species [27]. Similarly, measureable increases in antioxidant activities and oxidative stress have been demonstrated between pregnant and non-pregnant women [28], and inadequate trophoblast invasion, placental suboptimal perfusion, and ischemia in pre-eclampsia resulted in changes in maternal circulation that reflected increased oxidative stress [29,30]. Hence, changes in oxidant and antioxidant activities likely play significant roles in the pathophysiology of basic hypertension and pre-eclampsia.

Increased Cu and decreased Zn levels were observed in healthy pregnant women compared with non-pregnant women, and in eclamptic pregnant women compared with healthy pregnant and non-pregnant women. Because Cu and Zn are present in combination in various first-step antioxidant enzymes, increases in Cu/Zn ratios may lead to inactivation of antioxidant enzymes and oxidative stress [10]. Moreover, significantly greater induction of oxidative stress was observed in eclamptic patients than in subjects with normal pregnancies, suggesting a role in abnormal placentation and endothelial damage, and hence the etiology of pre-eclampsia, presumably reflecting the increased presence of LPOs [11].

Low [31] or unchanged [32] serum Zn levels in the placenta have been reported in cases of pre-eclampsia. Moreover, decreased

serum Zn concentrations in pre-eclampsia reportedly reflect reduced levels of estrogen and Zn binding protein [33]. Previous studies also report increased Cu concentrations in pre-eclampsia [10], whereas others show decreased [34] or unchanged Cu levels [35]. In agreement with İlhan et al. [37], increased Cu levels and decreased Zn levels were identified in the present PE group compared with those in HP and NP groups, and in the HP group compared with the NP group. Taken together, these data indicate that PE is mediated in part by the LPO product MDA, and is indirectly associated with SOD activity and the presence of Cu, which has pro-oxidant features and plays a role in the activity of first-step antioxidant enzymes, and Zn, which is a structural cofactor of many antioxidant enzymes.

In an early study by Ajose et al. [37], Cu/Zn ratios were significantly higher in pregnant women than in non-pregnant women, and increased with duration of gestation. In contrast, Kumru et al. showed lower Cu/Zn ratios in PE patients than in healthy pregnant females [34], and Fenzl et al. reported significantly higher Cu/Zn ratios in healthy pregnant women, women with gestational hypertension, and PE patients than in the healthy controls [9]. Similarly, the present data show significantly higher Cu/Zn ratios in healthy pregnant females than in non-pregnant females, and in PE patients than in non-pregnant and healthy pregnant women. In a study by Karahan et al., Cu/Zn ratios were more indicative of vascular endothelial damage and vascular complications than Cu and Zn levels alone [38], potentially reflecting the relative presence of these metals as cofactors for antioxidant enzymes. Accordingly, we determined whether Cu/Zn ratios are indicative of vascular damage and fetal birth weights, and although no correlations were observed in the healthy pregnant group, increased Cu/Zn ratios were correlated with decreased fetal birth weights in pre-eclamptic women. In contrast, no correlations were identified between indices of Cu, Zn, MDA, and SOD and birth weights, suggesting that Cu/Zn ratios are solely predictive of vascular damage and may affect fetal growth. Although the prognostic value of the Cu/Zn ratio has been previously investigated in breast cancer [39] and Hodgkin's disease [40] patients, the present data are the first to show an association of Cu/Zn ratios and with fetal birth weights.

Evidence of functional impairment of placental vasculature in pregnancies with interuterine growth restrictions (IUGR) is compelling, although the effects of maternal overweight and obesity on PE remain poorly understood [41]. Nonetheless, recent data also suggests that markers of inflammation [42] and oxidative stress [43] are increased in the placenta during PE pregnancies in obese women. Specifically, relaxation of chorionic plate arteries from placentae of obese women in response to exogenous nitric oxide (NO) was reportedly limited in comparison with that in placentae from women with normal BMI [43], suggesting altered vascular function. Accordingly,

the free radical NO is a key vasodilator of the placental vascular bed, and is synthesized mainly by endothelial NOS (eNOS) in response to shear stress and vasoactive molecules such as the calcitonin-gene related peptide [44]. Notably NO synthesis is strongly reduced by stress, and subsequent placental exposure to the pro-oxidant peroxynitrite increases perfusion pressure and limits relaxation in response to exogenous NO [45]. In addition, Schneider et al. showed that oxidative stress and the related placental endothelial dysfunction may cause IUGR and low birth weight babies [46]. Taken together, these data indicate that oxidative stress plays key roles in vascular dysfunction of IUGR placental vessels, and increases contractile responses [41,42].

The present study was limited to 120 patients and oxidative stress and vascular damage was not evaluated in placental tissue using histopathological or biochemical methods, which may corroborate the present observations of maternal serum. In addition, only late initiation preeclamptic pregnancies at >32 weeks gestation were included in the study cohort, and only selected trace elements, antioxidants, and oxidants were investigated. Hence, further analyses of trace elements and molecules that have demonstrated roles in oxidative stress are warranted.

Conclusions

Imbalances between lipid peroxides and antioxidants in blood may contribute to cytotoxic mechanisms that cause endothelial cell injury. The present data suggest that elevated Cu/Zn ratios inactivate antioxidant enzymes such as Cu/Zn SODs, and the ensuing increases in lipid peroxidation and impairments of antioxidant defense systems are associated the pathogenesis of pre-eclampsia. Hence, Cu/Zn ratios may be predictive of vascular complications during pre-eclamptic pregnancies.

Conflict of interest

The authors have no conflict of interests to declare.

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