RESEARCH ARTICLE / Araştırma Makalesi

The Role of Maternal Oxidative Stress, Iron/Zinc, Copper/Zinc Ratios and Trace Element Levels in the Pathogenesis of Preeclampsia

Preeklampsinin Patogenezinde Maternal Oksidatif Stres, Demir/Çinko, Bakır/Çinko Oranları ve Eser Element Düzeylerinin Rolü

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Özet

Purpose: Preeclampsia (PE) is a complex disease and the underlying mechanisms are not known, yet. It is well known that oxidative stress and trace elements play a role in the pathogenesis of various diseases. Several studies have shown that the levels and proportions of trace elements are closely related to the severity of the disease. The aim of the study was to investigate the changes in some characteristics parameters, serum zinc, iron, copper levels, and copper/zinc and iron/zinc ratios and plasma lipid peroxidation levels in patients with mild and severe preeclampsia.

Materials and Methods: Ninety healthy pregnant women and 80 pregnant women with PE which are classified as mild (n=36) and severe (n=44) preeclamptic subgroups were included. Serum copper, zinc and iron were measured by atomic absorption spectroscopy (AAS) and iron/zinc and copper/zinc ratios were calculated. Plasma malondialdehyde (MDA) levels were analyzed by spectrophotometric method.

Results: Plasma MDA, serum iron/zinc and copper/zinc ratios, serum copper and iron levels were found to be increased in the PE group compared to the healthy pregnant group. Serum zinc levels decreased significantly in the PE group. Serum zinc levels in severe PE group, but not in mild PE, were found to be significantly lower compared to healthy pregnant women. Serum iron levels were found to be higher in mild PE group compared to healthy pregnant control group. Serum copper and copper/zinc ratios were found to be higher in the mild and severe PE groups compared to the control group. Serum iron/zinc ratios were found to be higher in the severe PE group than in the healthy control group.

Conclusion: Our study has shown that oxidative stress and trace elements play a role in the etiopathogenesis of PE. İnteractions of both trace element levels and their ratios with underlying mechanisms of PE should be clarified in details with further studies. **(Sakarya Med J 2017, 7(1):26-32)**

Key words: Preeclampsia, malondialdehyde, copper, zinc, iron, copper/zinc, iron/zinc

Abstract

Amaç: Preeklampsi (PE) kompleks bir hastalıktır ve hastalığın patogenezinde yer alan mekanizmalar henüz aydınlatılamamıştır. Oksidatif stres ve eser elementlerin çeşitli hastalıkların patogenezinde rol oynadığı iyi bilinmektedir. Yapılan çeşitli çalışmalarda, eser elementlerin düzeylerinin ve oranlarının, hastalığın şiddeti ile yakından ilişkili olduğunu göstermiştir. Bu çalışmanın amacı, hafif ve şiddetli preeklamptik hastalarda bazı karakteristik özelliklerin, serum çinko, demir, bakır düzeyleri, bakır/çinko ve demir/çinko oranları ile plazma lipid peroksidasyon düzeylerini değişikliklerini araştırmaktır.

Gereç ve Yöntem: Çalışmaya 90 sağlıklı gebe ve 80 preeklamptik gebe dahil edildi. Preeklamptik gebeler hafif (n=36) ve ağır (n=44) olmak üzere iki alt gruba ayrıldı. Serum bakır, çinko ve demir düzeyleri atomik absorpsiyon spektroskopisi (AAS) ile ölçüldü ve demir/çinko ve bakır/çinko oranları hesaplandı. Plazma malondialdehit (MDA) düzeyleri spektrofotometrik yöntem ile ölçüldü.

Bulgular: Plazma MDA, serum demir/çinko ve bakır/çinko oranları, serum bakır ve demir düzeylerinin PE grubunda sağlıklı gebe grubuna göre artmış olduğu tespit edildi. Serum çinko düzeyleri PE grubunda anlamlı olarak daha düşüktü. Ancak serum çinko düzeyleri ağır ve hafif PE gruplara ayrılarak sağlıklı gebelerle karşılaştırıldığında ağır PE grup anlamlı olarak düşük bulunmakla birlikte hafif PE grup sağlık gebelerden istatistiksel olarak farklı değildi. Serum demir düzeylerinin hafif PE grupta sağlıklı gebe kontrol grubuna göre yüksek olduğu tespit edildi. Serum bakır ve bakır/çinko oranlarının hafif ve ağır PE grupların her ikisinde de kontrol grubuna göre yüksek olduğu saptandı. Serum demir/çinko oranları ise sadece ağır PE grupta sağlıklı kontrol grubuna göre yüksek bulundu.

Sonuç ve Yorum: TÇalışmamızda oksidatif stresin, eser elementlerin PE etyopatogenezinde rol oynadığı gösterilmiştir. Bu hastalıkta gerek çinko bakır demir gibi eser elementlerin düzeylerinin gerekse demir/çinko ve bakır/çinko gibi bu elementlerin oranlarının hastalığın etyopatogenezi yer alan mekanizmalarla etkileşiminin aydınlatılması için daha ileri çalışmalara ihtiyaç duyulmaktadır. **(Sakarya Tıp Dergisi 2017, 7(1):26-32)**.

Anahtar kelimeler: Preeklampsi, malondialdehit, bakır, çinko, demir, bakır/çinko, demir/çinko

Introduction

Preeclampsia (PE), a unique hypertensive disorder of human pregnancy, is a major cause of maternal and perinatal mortality and morbidity. It affects approximately 5 % of pregnancies worldwide. Despite the extensive research, its etiology and pathogenesis still remain unexplained and it cannot be treated effectively, yet.[1] There are some pathophysiological conditions associated with increased oxidative stress in pregnancies, including miscarriages, preeclampsia, gestational diabetes mellitus (GDM), and intra-uterine growth restriction. Preeclampsia is a clinical condition of human pregnancy, characterized by hypertension and proteinuria and regressing after birth. Many studies have reported that there is an imbalance between the production of reactive oxygen species (ROS) and anti-oxidants, repair processes. Proteins, lipids and DNA are all vulnerable to oxidative damage which has been implicated in the etiology of a wide variety of chronic and acute diseases[2]. Several reports have suggested that blood and placental levels of oxidative damage markers are increased in women with preeclampsia. Increased production of free radicals cause endothelial dysfunction.[3-6] Poorly perfused placental tissue may evoke the free radical process and the inception of generalized lipid peroxidation. Production of free radicals in endothelial cells is relatively low in normal conditions due to active defense systems, including chemical scavengers or antioxidant molecules and enzymes, such as reduced glutathione, superoxide dismutase, catalase, glutahione reductase and glutathione peroxidase. The changes in circulating levels of these antioxidant markers suggesting increased oxidative stress in patients with preeclampsia.[7-9]

Trace elements are necessary to biological processes in human health. However, an overabundance or a deficiency of trace elements may lead to various diseases. Some trace elements are toxic while others are known to possess anti-inflammatory and antioxidant properties. Disturbance of trace element status increase the risk of many diseases, yet there are very few studies which look into the way it occurs.[10] Zinc (Zn) is a component of more than 3000 zinc-associated transcription factors, including DNA-binding proteins with zinc fingers, and more than 300 enzymes, including copper/zinc superoxide dismutase and several proteins involved in DNA repair. Thus, Zn plays an important role in protecting cellular components from oxidation and its damage to biomolecules.[11] Zn and copper (Cu), the essential elements normally associated with metallothioneins, are held in intracellular reservoir for metalloproteins. In cells exposed to toxic divalent heavy metals, an isoform of metallothioneins can sequester these elements and diminish the acute effects of the metals. They can also act as a scavenger of reactive oxygen and nitrogen species so regulate cellular redox potential. Cu, as transition metal, can promote free radicals formation, catalyzing the reaction between the superoxide anion and hydrogen peroxide producing the hydroxyl radical. Furthermore, Cu can bind directly to free thiols of cysteines, leading to oxidation and crosslinks between proteins, thus inactivating enzymes or impairing structural proteins. The trace element of Cu in its ionic form rapidly becomes toxic to a variety of cells. Cu is an important element for numerous metalloenzymes and metalloproteins, such as superoxide dismutase, cytochrome oxidase, lysine oxidase, dopamine- -hydroxylase, and ceruloplasmin. On the other hand, Fe is mostly bound to transferrin. It is needed for hemoglobin, myoglobin, cyclo-oxygenases, cytochromes, many hydoxylase/oxidase enzymes, ribonucleotide reductase, aconitase, succinate dehydrogenase, catalase, and many others.[10,12] Several trace elements and oxidant/antioxidant status have been implicated in the pathogenesis of preeclampsia.[13-16] In several of studies, trace element ratios have been used as an index related to increased inflammation and oxidative stress in the development or progression of the disease activities. However, there are various of studies in the literature, in which preeclamptic patients disclose the relationship of some characteristic features, trace element levels and oxidative stress parameters. The findings of these studies also appear to be contradictory.

Therefore, in the present study, our aim was to investigate the changes in some characteristics parameters, serum zinc, iron, copper levels, and copper/zinc and iron/zinc ratios and plasma lipid peroxidation levels in patients with mild and severe preeclampsia.

Materials and Methods

Women were examined between April 2015 and September 2016, and comprised 170 primiparous singleton pregnancies.

Gestational age was established on the basis of menstrual dates and confirmed by first trimester ultrasonography. Differential diagnosis of PE was made according to the current American College of Obstetricians and Gynecologists (ACOG) guidelines.[17] These guidelines define PE as sustained pregnancy-induced hypertension with proteinuria. Protocol of screening and diagnosis of PE were adapted from the guidelines and protocols from Department of Obstetrics and Gynecology, Cerrahpasa Medical Faculty, Istanbul University, Istanbul, Turkey. Hypertension was defined as sustained blood pressure readings of ≥140/90 mm Hg (with reading taking place >6 h apart). ACOG defines proteinuria as urine protein concentrations of ≥300 mg/day (or 1+ on a urine dipstick) on two or more random specimens collected >4 h apart. The criteria for distinguishing severe preeclampsia from mild preeclampsia were a blood pressure greater than 160/110 mmHg or proteinuria greater than 3+ on the dipstick, as suggested by Bolte et al.[18] All of the subjects were submitted to uterine artery Doppler and maternal echocardiography at 24 weeks gestation. All participants, patients and healthy controls were of Turkish origin, from Istanbul. Exclusion criteria for all subjects were tobacco use, twin pregnancies, preexisting maternal chronic medical problems, chromosomal or suspected ultrasound fetal abnormalities, maternal heart disease, and use of antihypertensive medication, diabetes mellitus and renal disease at the 1-year follow-up visit. Patients were followed until term to verify the fetoneonatal and maternal outcomes. The evolution of gestation was followed until term by an investigator, blinded to the results of maternal echocardiography. All participants were informed about the survey and freely signed and dated the consent form. The protocol was approved by the Ethics Committee of Medical Faculty in Sakarya University and was conducted in accordance with the Declaration of Helsinki (16214662/050.01.04/67).

Medications were ceased at least 24 hours before the blood collection. Blood samples were collected in EDTA-containing tubes and anticoagulant-free tubes after an overnight fasting. After immediate centrifugation (3.000xg) for 10 min at 4 oC, plasma and serum samples were separated in eppendorf tubes and frozen immediately at -80 oC until analysis.

The Cu, Fe and Zn levels of serum were measured by a flame atomic absorption spectrophotometer (Shimadzu AAS-6800, Tokyo, Japan). Cu, Fe and Zn stock standards (of concentration 1000 ppm) were obtained from Merck (Darmstadt, Germany). Results were calculated as micrograms per deciliter in serum samples. Iron/zinc and copper/zinc ratios were calculated.

The lipid peroxide levels in plasma samples were measured using a thiobarbituric acid reactive substance (TBARS) assay, which monitors MDA production, based on the method of Beuge and Aust.[19] The amount of MDA was calculated using an extinction coefficient (1.56×10−5 M/cm). The concentrations of MDA were expressed as micromoles per liter plasma samples.

Results are shown as mean±SD. Statistical analysis was performed using SPSS 17.0 statistical software for Windows (SPSS, Chicago, IL, USA). The non-parametric test (Mann-Whitney U test), parametric test (independent samples t test), one-way ANOVA test and Tukey's HSD post hoc test were performed for the analysis of MDA, Cu, Fe and Zn levels, and Cu/Zn and Fe/Zn ratios and clinical characteristics parameters. The results were evaluated in confidence interval of 95 % and statistical significance of $p<0.05$.

Results

Some characteristic features of preeclamptic pregnant patients group and healthy pregnant control group were given in Table 1. Ages of PE and control groups were 29.87±5.25 and 31.76±5.87 respectively. In the hypertension parameters, systolic blood pressure ($p<0.001$) and diastolic blood pressure ($p<0.001$) were significantly higher in the preeclamptic patients compared to the control group. Fetal weight ($p<0.001$) were significantly lower in the in the preeclamptic patients compared to the control group. Body mass index were not statistically different between two groups of the study.

Zinc levels (77.59±30.49 µg/dl) of the preeclamptic pregnancy patients were significantly lower compared to the healthy pregnancy group (91.03±30.59 µg/dl) ($p<0.004$) (Table 2). As a maker of oxidative damages, MDA levels were higher in PE patients (4.98±1.45) than controls (4.52±1.50). The difference was statis

tically significant (p<0.048). Iron, copper levels, and iron to zinc ratio (Fe/Zn) and copper to zinc ratio /Cu/Zn) were also significantly higher in preeclamptic pregnancy patients group (p<0.001, p<0.001, p<0.001, p<0.001, respectively). Table 3 shows the clinical characteristic parameters in the mild and severe preeclamptic groups and healthy pregnancy groups. Systolic blood pressure and diastolic blood pressure were significantly increased, and fetal weight were significantly decreased in both the mild and severe preeclamptic patients groups compared with those of healthy pregnancy group (p<0.001, for each).

Table 1. Clinical characteristics of preeclamptic and healthy pregnant groups (M±SD)

Parameters	Control Group	Preeclamptic Patient Group	p value
Age (year)	29.87±5.25	31.76±5.87	0.020
BMI (kg/m2)	27.89±3.96	31.33±4.14	0.390
SBP (mm Hg)	107.76±16.41	155.89±14.7	0.001
DBP (mm Hg)	68.57±11.67	101.93±11.25	0.001
Fetal weight (g)	3146.44±544.43	1883.53±1026.16	0.001

SBP:Systolic Blood Pressure (mm Hg); DBP: Diastolic Blood Pressure (mm Hg)

Table 2. The mean levels of MDA in plasma, Zn, Cu, Fe levels and Fe/Zn and Cu/Zn ratios in serum samples of patients with preeclampsia and healthy pregnant control groups (M±SD)

Parameters	Control Group	Preeclamptic Patient Group	p value
Zn (µg/dl)	91.03±30.58	77.59±30.49	0.004
Fe (µg/dl)	241.45±41.61	269.88±50.77	0.001
Cu (µg/dl)	202.13±48.31	272.49±74.50	0.001
Fe/Zn	2.60±0.97	3.68±1.35	0.001
Cu/Zn	2.39±0.74	3.82±1.44	0.001
MDA (µmol/l)	4.52±1.50	4.98±1.45	0.048

We also examined the change of trace elements and ratios, MDA and some other parameters according to the mild and severe preeclamptic status (Table 4). Serum zinc levels were significantly decreased in the severe preeclamptic group (74.92±27.78) compared with healthy pregnancies (91.03±30.58) (p<0.017). Serum iron concentrations in the mild preeclamptic group (277.89±46.20) were significantly higher than those of the healthy pregnant group (241.45±41.61) (p<0.002). Serum copper and Cu/Zn ratios were found to be higher in the mild (281.39±71.68, 3.86±1.42, respectively) and severe preeclamptic groups (262.86±77.24, 3.79±1.48, respectively) compared to the control group (202.13±48.32, 2.39±0.74, respectively) (p<0.001, for each). Serum Fe/Zn were found to be higher in the severe preeclamptic group (3.90±1.42) than in the healthy control group (2.91±0.98) (p<0.001).

Discussion

Findings of our study indicated that systolic blood pressure and diastolic blood pressure, plasma MDA, serum Fe/Zn and Cu/Zn ratios, serum copper and iron levels were significantly higher in the preeclamptic patients compared to the control group. However, fetal weight and serum zinc levels were significantly lower in the in the preeclamptic patients compared to the control group. Also, serum zinc levels were found to be significantly lower in the severe preeclampsia group than in the healthy pregnancy group. Serum iron levels were found to be higher in mild preeclamptic group compared to healthy pregnant control group. Serum copper and Cu/Zn were found to be higher in the mild and severe preeclamptic groups compared to the control group. Serum Fe/Zn ratios were found to be higher in the severe preeclamptic group than in the healthy control group.

Table 3. Clinical characteristics of mild and severe preeclamptic and healthy pregnant groups (M±SD)

Parameters	Control Group	Mild Preeclamptic Patient Group	Severe Preeclamptic Patient Group	[a]p	[b]p	[c]p
Age (year)	29.87±5.25	32.50±5.48	30.83±6.27	0.017	0.613	0.318
BMI (kg/m2)	27.89±3.96	31.47±4.13	31.16±4.19	0.001	0.001	0.927
SBP (mm Hg)	107.76±16.40	147.12±6.67	166.25±13.47	0.001	0.001	0.001
DBP (mm Hg)	68.57±11.67	97.02±7.56	107.73±12.17	0.001	0.001	0.001
Fetal weight(g)	3147.44±544.43	2304.43±1028.36	1395.66±786.49	0.001	0.001	0.001

SBP:Systolic Blood Pressure (mm Hg); DBP: Diastolic Blood Pressure (mm Hg)
[a]p; control group vs. mild preeclamptic group, [b]p; control group vs. severe preeclamptic group, [c]p; mild preeclamptic group vs. severe preeclamptic group

Table 4. The mean levels of MDA in plasma, Zn, Cu, Fe levels and Fe/Zn and Cu/Zn ratios in serum samples of patients with mild and severe preeclamptic and healthy pregnant control groups (M±SD).

Parameters	Control Group	Mild Preeclamptic Patient Group	Severe Preeclamptic Patient Group	[a]p	[b]p	[c]p
Zn (µg/dl)	91.03±30.58	80.14±33.00	74.92±27.78	0.139	0.017	0.726
Fe (µg/dl)	241.45±41.61	277.89±46.20	261.87±54.87	0.002	0.132	0.460
Cu (µg/dl)	202.13±48.32	281.39±71.68	262.86±77.24	0.001	0.001	0.382
Fe/Zn	2.91±0.98	3.46±1.28	3.90±1.42	0.084	0.001	0.367
Cu/Zn	2.39±0.74	3.86±1.42	3.79±1.48	0.001	0.001	0.963
MDA (µmol/l)	4.53±1.50	5.03±1.59	4.92±1.29	0.165	0.359	0.939

SBP:Systolic Blood Pressure (mm Hg); DBP: Diastolic Blood Pressure (mm Hg)
[a]p; control group vs. mild preeclamptic group, [b]p; control group vs. severe preeclamptic group, [c]p; mild preeclamptic group vs. severe preeclamptic group

Although the causes of preeclampsia 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.[16,20] It has been suggested that transition metals, such as Fe and Cu, may participate in the oxidative damage of cells and tissues. According to previous studies serum levels of some oxidant antioxidant and trace element status changed in PE patients.[3,9,14,15,16,20] To understand roles of trace elements in etiopathogenesis of PE, especially in terms of the severity of the disease, serum Fe, Cu and Zn levels, Fe/Zn, Cu/Zn ratios, plasma MDA levels and some clinical parameters were determined in patients with PE classified as mild and severe according to their symptoms. In the literature, pregnancy related diseases such as gestational diabetes and preeclampsia have been associated with disturbed trace element status and oxidant/antioxidant balance. To our knowledge, our study is unique by searching the relationship between lipid peroxidation, Cu, Fe, Zn levels, Fe/Zn, Cu/Zn ratios and some clinical parameters in terms of the severity of the symptoms in patient with preeclampsia.

The disturbance of the prooxidant/antioxidant balance that results from increased free radical production, antioxidant enzyme inactivation, and excessive antioxidant consumption is the causative factor in oxidative damage. Oxidative stress is an important mediator of abnormal platelet function and dysfunctional endothelium-dependent vasodilation in the setting of cardiovascular disease. The malondialdehyde, a carbonyl group produced during lipid peroxidation, is used widely in determining oxidative stress. In several studies, increased serum MDA levels in many diseases were reported.[16,20,21-23] In our study, we found increased plasma MDA levels in preeclamptic patients compared to healthy pregnant controls. İn the literature, it also has been implicated that transition metals, such as Cu and Fe played role in production of oxidative damages in many diseases.[24,25] Free radicals can damage many different biomolecules, and the initial target of oxidation varies with the type of cell, location of oxidative stress, its severity, and the availability of metal ions.[24] Exposure to metals such as, Fe and Cu, leads to molecular damages and alternation of cell homeostasis due to free radicals produced via Fenton-like reactions. Zn may function as an antioxidant by two mechanisms. It can increase iron and copper availabilities by competing for their binding proteins. Moreover, Zn binds the sulfhydryl groups in proteins, protecting them from oxidative damage. The levels of trace elements in circulating blood have traditionally been used for diagnosing many diseases. Fenzl et al. found that serum Cu and total serum oxidant capacity were significantly higher while Zn was lower in all pregnant groups regardless of hypertensive disorders.[14] Moreover, they reported that serum Fe and total serum antioxidant capacity levels were found to be significantly higher in pregnant women with preeclampsia compared to pregnant controls. Bakacak et al. shown that serum Zn levels were significantly lower in the PE group than in healthy pregnant women and non-pregnant women groups.[15] In contrast, they have found that Cu, Zn, and MDA levels and Cu/Zn ratios were significantly higher in the PE group than healthy pregnant women and non-pregnant women groups. In our study, serum Cu and Fe levels were higher and serum Zn levels were lower in PE patients group when compared to healthy pregnancy controls.

Endothelial dysfunction in human occurs in various inflammatory conditions, angiogenesis, oxidative damage, hypoxia, and mechanical stress. All these complex processes may show even more complex interactions with the status of trace elements. Any condition associated with increased oxidative stress or inflammation might be expected to decrease Zn levels. This is probably due to increased consumption of Zn as an antioxidant element. Due to the inverse relationship between copper and zinc levels, increased copper levels in serum were also an expected finding in preeclampsia. In our study, serum Fe levels were also increase, likewise copper. Moreover, together with high Cu, Fe and low Zn levels in serum, serum Fe/Zn, Cu/Zn ratios were increased in our patients reflecting increased or ongoing inflammation and/or oxidative damage processes in this disease. Several studies have reported that some trace elements ratios together with trace element levels were more sensitive indicator for monitoring inflammation and/or oxidative stress in terms of the severity of the disease.[26,27] Despite conflicting findings in the literature, these reports seem to support our results.

Additionally, we found that systolic blood pressure and diastolic blood pressure were significantly increased, and fetal weights were significantly decreased in both the mild and severe preeclamptic patients groups compared with those of healthy pregnancy group. We also showed that serum zinc levels were significantly decreased in the severe preeclamptic group compared with healthy pregnancies, but serum iron concentrations were significantly higher in the mild preeclamptic group than those of the healthy pregnant group. Serum copper and copper/zinc ratios were found to be higher in the mild and severe preeclamptic groups compared to the control group. Serum iron/zinc ratios were found to be higher in the severe preeclamptic group than healthy control group. In many studies oxidative stress is associated with fetal development, so we thought that oxidant/antioxidant status and trace element distribution may be involved in the occurrence of preeclampsia or its complication.

In our study, we found increased plasma MDA levels in PE patients. Based on the findings of our study, we conclude that circulating of copper, zinc, iron levels and Fe/Zn, and Cu/Zn ratios and MDA levels might be involved in etiopathogenesis of preeclampsia as reason or result. Further study is required to determine the exact mechanisms of the redox-active transition metals and oxidative stress in preeclampsia.

Conflict of interest

The authors declare that they have no conflicts of interest related to the publication of this manuscript.

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