Original Article

Evaluation of 24-Hour Urine Copper in Preeclamptic Vs. Normotensive Pregnant and Non-Pregnant Women

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Abstract

Background: The aim of this study was to evaluate copper status in women with preeclampsia.

Materials and Methods: Sixty preeclamptic, sixty normotensive pregnant and sixty healthy non-pregnant women were enrolled in a cross sectional study. The 24-hour urine copper was compared among the women.

Results: There was significant difference in the copper concentration of 24-hour urine among the three groups due to the difference between preeclamptic and normotensive pregnant women (12.19±3.71 vs. 5.69±2.05, $p<0.001$).

Conclusion: The results of this study revealed that the level of urine copper increases preeclamptic pregnancy. Prospective studies are needed to determine whether observed alternation in copper precede preeclampsia or the difference may be attributed to preeclampsia-related alternations in maternal trace metal metabolism.

Keywords: Copper, Preeclampsia, Pregnancy

Introduction

Preeclampsia is defined as the onset of proteinuric hypertension after mid-pregnancy; a systemic disease of the later stages of pregnancy that affects about 6% of pregnant women. Although it is an important cause of fetal and maternal morbidity, its etiology is still under investigation (1).

Copper, a component of numerous metalloenzymes and cofactor for the antioxidant enzyme superoxide dismutase, is known to affect the level of norepinephrine and dopamine in the brain (2). Serum copper level increases from about 80-155 mg/dl before pregnancy to about 118-302mg/dl by the end of the third trimester. The physiologic increase in copper concentration in pregnancy is, in parts associated with estrogen induction of copper-carrying protein .There is considerable inconsistency in the results concerning the relation between maternal plasma copper concentrations and preeclampsia (2-12).Accordingly and since the level of copper in serum may fluctuate during the day, in the present study we attempted to assess 24-hour urine concentration of copper in preeclamptic women using normotensive and non-pregnant controls.

Materials and Methods

In an analytical cross-sectional study, the 24-hour urine concentration of copper was measured in 63 women with preeclampsia who referred to the Kosar Medical University Center and had the inclusion criteria (case group), 63 matched women with uncomplicated pregnancy (control 1) and 60 normotensive, nonpregnant women (control 2). The women were matched for age, body mass index (BMI), socioeconomic status in the three groups, and gravidity and gestational age in preeclamptic and healthy pregnant women. Preeclampsia is defined as persistent (6 hours or more) blood pressure of at least 140/90 mmHg with proteinuria (urine protein concentration of 300 mg/daily or more). At the beginning of the study, a questionnaire was used to gather the information about socioeconomic status of the women including their living place and the data about their copper consumption. Then, the women were excluded if :they use water from copper water pipes, cooked in copper ware, had a high-copper diet, used birth control pills or copper intrauterine devices for contraception. Women with serious health problems, such as diabetes, epilepsy, renal disease, and RH-factor problems were excluded from the study.

To exclude chronic hypertension the women were followed-up until three months after delivery. The women with preeclampsia were divided into mild and severe preeclamptic patients based on indications of severity (Table 1).

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Table 1: Indications of severity of hypertensive disorders during pregnancy

Abnormality	Mild	Severe
Diastolic blood pressure	<100 mm Hg	110 mm Hg or higher
Proteinuria	Trace to 1+	Persistent 2+ or more
Headache	Absent	Present
Visual disturbances	Absent	Present
Upper abdominal pain	Absent	Present
Oliguria	Absent	Present
Convulsion(eclampsia)	Absent	Present
Serum creatinine	Normal	Elevated
Thrombocytopenia	Absent	Present
Liver enzyme elevation	Minimal	Marked
Fetal growth restriction	Absent	Obvious
Pulmonary edema	Absent	Present

Copper concentration in 24-hour urine of all the women was measured by atomic absorption spectrometry at the beginning of the study. Twenty-four hour urine protein-excretion and serum liver enzymes were measured along with the copper and whenever it were necessary.

Six women were excluded due to unknown congenital abnormalities and chronic hypertension. Finally, the data of 180 women (60 in each group) were analyzed.

The study was approved by the Review Board for Research on Humans in the University of Tarbiat Modares, and all of the women gave a written consent for their participation.

One-way Analysis of Variance (ANOVA) using Least Significant Difference (LSD) ,T student test, Kruskal Wallis test and χ^2 test were used for the comparison of the parameters. Spearman's correlation coefficient was used for evaluation of the relation between copper and protein concentrations in the 24-hour urine.

Statistical significant was at a $p<0.05$.

Results

Although, no significant differences in the socio-demographic and obstetric parameters were found among the three groups, there was a significant difference in urine copper concentration (Table 2).

Table 2: Demographic and obstetrics parameters in the three groups at the beginning of the study

	Case (n=63) preclamptic patients	Control 1(n=63) healthy pregnant women	Control 2(n=60) healthy nonpregnant women	P
Age*(year) Mean ± SD	25.42 ± 3.70	25.13 ± 3.91	25.57 ± 3.43	N.S
Job n(%) Housewife**	59(94%)	58(92%)	56(93%)	N.S
employee	4 (6%)	5 (8%)	4(7%)	
BMI* Mean±SD	23.51 ± 0.18	23.45 ± 0.17	23.47 ± 0.17	N.S
Gravidity* Median (range)**	1(1-3)	1(1-3)	2(1-3)	N.S
Gestational** Age(week) Mean±SD**	34.70 ± 0.50	34.27 ± 1.90	-	N.S
Copper in 24-hour* Urine (mg/lit) Mean±SD	12.19 ± 3.71	5.69 ± 2.05	5.31 ± 1.51	<0.001

* ANOVA test with LSD

** χ^2 test

*** Kruskal Wallis

****T student test

Table 3: Comparison of outcome of pregnancy among the two groups

	Preclamptic patients Case (n=63)	Healthy pregnant women Control (n=63)	P
Gestotional age at the time of delivery (weeks) Mean±SD**	35.2 ± 2.3	39.3 ± 1.1	<0.001
Method of delivery* n (%) Vaginal**	31(52%)	50(83%)	
Cesarean	29(48%)	10(17%)	<0.001
Birth weight (g) Mean±SD**	2400 ± 742	3460 ± 292	<0.001
Apgar score<5* n (%)**	13(21.5%)	1(1.6%)	<0.001

* ANOVA with LSD
** T student test
*** χ^2 test

Table 4: Comparison of copper,liver enzymes, and protein concentration in 24-hour urine between the mild and severe preclamptic women and their correlations

	Mild preeclampsia (n=32)	Severe preeclampsia (n=28)	P
Copper in 24-hour* Urine (mg/lit) Mean ± SD	12.92±3.48	11.46±3.88	NS
Protein in 24-hour* Urine (mg/lit) Mean ± SD	327.60±34.04	1680.33±268.80	<0.001
SGPT* (U/lit)	28.6±7.6	55.5±10.4	<0.001
SGOT* (U/lit)	26.5±6.9	57.2±11.8	<0.001

* T test

Also, there were significant differences in gestational age at delivery, method of delivery, birth weight, and Apgar score between the preeclamptic group and the normotensive pregnant group (Table 3). No correlation was found between the 24-hour urine copper and protein concentrations in preeclamptic women (r=-0.187,P=0.153). There were significant differences in protein and serum liver enzymes but not in copper urine concentrations between the mild and severe preeclamptic women. (Table 4).

Discussion

Preeclampsia is associated with an imbalance of increased lipid peroxides and decreased antioxidants (1). Ceruloplasmin (CP) acts as an antioxidant by several mechanisms (12). About 90 percent of copper in the blood is in the form of ceruloplasmin. Excess copper is eliminated mainly through the liver into the bile and lost through the intestines. A minimal amount is excreted in the urine.

There are reports that maternal serum copper level is lower in preeclamptic women as compared to healthy controls (4,12).This finding is supported by the decreasing trend in the level of free estriol (which induces the production of copper carrying protein) among preclamptic women(13).A few recent reports have shown increasing of copper concentrations (as the co-factor of antioxidant enzymes) and also oxidant and antioxidant parameters in preeclamptic pregnant women .It was suggested that copper shows contrary kinetic behavior during the entire pregnancy as compared with the corresponding zinc values (5, 6, 10). Differences in study design, limited statistical power, differences in tissues and analytical techniques used to measure maternal copper status, as well as differences in exposure to environmental copper, like different maternal dietary intakes, are possible explanations for this difference.Also, Vari-

ation in gestational-age specific plasma volume expansion, the well-characterized hypovolumenia in preeclamptic versus normotensive pregnancies and copper levels measured in serum may lead to some daily fluctuation may have introduced increased variability in maternal plasma or serum copper concentration in previous studies. Another explanation for this inconsistency in the results, might be due to the compensatory response to increased peroxidation and, therefore, elevation of serum copper level at the beginning of the disease . However, after placental insufficiency in advanced preeclampsia followed by decreasing free estriol level, serum copper level decreases.

The results of this study revealed that the level of urine copper which are the co-factor of antioxidant super oxidedismutase increases in mild and severe preeclamptic pregnancy. Although , urine copper level was lower in severe preeclampsia as compared to mild preeclampsia and this finding may associated with placental insufficiency overcoming. This difference was not significant. There was no correlation between the 24-hour urine copper and protein concentration in preeclamptic women, then increased copper in the urine is not due to increased loss of ceruloplasmin in the urine due to proteinuria.In this study any exposure to unusual environmental copper was omitted .In addition we chose a reliable test with stable results during the day .A potential limitation of the present study is the retrospective design which did not allow assessment of whether the observed alteration in copper concentration preceded preeclampsia or if the difference was attributed to preeclampsia related alterations in maternal copper metabolism.

Conclusion

Data from prospective studies are needed to evaluate the longitudinal relation between maternal copper status and the risk of preeclampsia.

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