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Serum Copper and Serum Zinc in Preeclampsia: Cause or Effect?

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Authors' contributions

This work was carried out in collaboration between both authors. Author AAKS designed the study, data collection and collation of participants information, performed the statistical analysis and written the manuscript. Author ANS did critical review, final editing. Both authors read and approved the final manuscript.

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ABSTRACT

Background: Preeclampsia is multisystem disorder. Despite its prevalence and severity, the pathophysiology of this multisystem disorder is poorly understood. In concern regarding the increasing number of preeclamptic cases and lack of data about the levels of trace elements in preeclampsia, a case-control study was conducted with aim to determine the trace elements like serum total copper and serum total zinc in preeclampsia.
Aims: To estimate alterations in serum copper and serum zinc in preeclampsia and to compare them with normal pregnant women.
Study Design: This is a case control study, carried out in the Department of Biochemistry, MIMER Medical College, Talegaon Dabhade, Pune.
Methods: The present study consisted of 120 study participants. These were divided into two groups. Group I - normal pregnant women as control (n=60) and Group II - preeclamptic group (n=60). The serum levels of copper and zinc were determined by inductively coupled plasma atomic emission spectrometry (ICP- AES) technique at IIT Mumbai.
Results: Analysis revealed that mean values of total serum copper and total serum zinc were 196.20 ± 25.9 and 77.15 ± 14.5 (µg/dl) respectively in control group. In preeclamptic group, the mean values of copper and zinc were 213.13± 38.6 and 76.23 ± 13.13 (µg/dl) respectively. Copper

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was significantly increased in preeclamptic group, while non-significant reduction in levels of zinc levels was observed when compared to control group.
Conclusion: In the present study, significantly high serum copper was observed in preeclamptic patients. Presence of high copper levels may be related factor in the etiopathogenesis of preeclampsia. Estimation of trace elements like copper and zinc may help clinicians in early diagnosis and minimizing or delaying complications of preeclampsia, hence preventing harm to both mother & fetus.

Keywords: Copper; zinc; preeclampsia; ICP- AES.

ABBREVIATIONS

Inductively Coupled Plasma atomic Emission spectrometer (ICP-AES)

- *(BP) Blood Pressure*

1. INTRODUCTION

Preeclampsia is a complex clinical syndrome that has been associated with severe maternal & fetal complications complications. It is characterized by increased blood pressure (BP), proteinuria, vasospasm, increased peripheral resistance and reduced organ perfusion [1]. It contributes to one of the top five causes of maternal and fetal morbidity and mortality [2]. According to National Health Portal (2016) the prevalence of hypertensive disorders of pregnancy was 7.8% and preeclampsia contribute to 5.4% of the study population in India [3]. The exact etiology of preeclampsia is still unknown. The most widely accepted theory being the defective implantation characterized by incomplete invasion of the spiral arteriolar wall by extravillous trophoblast resulting in a small calliber vessel with high resistance to flow [4,5,6].

Another possible hypothesis is concentrations of various trace elements are altered during pregnancy with changes in the mother's physiology and the requirements of growing fetus. Trace elements, needed in minute quantities, encompass minerals essential for normal human development and functioning of the body [7]. During pregnancy, inadequate stores or intake of trace elements can have adverse effects on both mother and fetus [8]. However their possible functions and contribution in determination of pregnancy disorders like preeclampsia has received insufficient attention particularly in this region. This study hence, tries to determine whether there was an alteration in maternal trace elements like serum copper and serum zinc and which may be related factors in pathogenesis of preeclampsia.

2. MATERIALS AND METHODS

A case control study was conducted in the Department of Biochemistry using clinical material from indoor patients (IPD) and outdoor patients (OPD) of Department of Obstetrics and Gynecology at MIMER Medical College and Bhausaheb Sardesai rural Hospital Talegaon (D) Pune from January 2013 - December 2016. As reported in the previous study by KS Meera, S Maitra and R Hemalatha [9] assuming an SD of HDL 3.56 in normal pregnancy and 3.53 in preeclamptic women, to detect a difference of 1.84 in the means of these groups the maximum estimated sample size was 120. Since this was an extension of another study sample size was calculated by HDL parameter on the basis of formula:

$$n = \frac{(Z\alpha/_2 + Z\beta/_2)^2 (SD_1^2 + SD_2^2)}{(m_1 - m_2)^2}$$

Where, $Z\alpha/_2$ = Area under normal curve for Type I error,
The alpha error = 0.05, value of $Z\alpha/_2 = 1.96$
Where, $Z\beta/_2$ = Area under normal curve for Type II error,
The Beta error = 0.2, value of $Z\beta/_2 = 1.28$

The maximum sample size was 120. Hence sixty preeclamptic patients and sixty healthy pregnant women were enrolled in the present study. Operational definition used for classifying study group include Group I: Normal pregnant women : Normal Blood pressure (BP) (≤120/80 mmHg) and presence of proteinuria after ≥ 20 weeks of gestation in women attending outdoor patient department (OPD) of Obstetrics and Gynecology and those admitted in ward were included as control. Group II: Preeclamptic women diagnosed as BP of ≥ 140/90 mmHg after ≥20 weeks gestation in a woman with previously normal BP and proteinuria [1]. These measurements were confirmed on at least 2 occasions 4-6 hour apart. According to American College of Obstetrics & Gynecology (ACOG),

diagnosis was confirmed by criteria of hypertension and proteinuria. Both primigravidas and multigravidas were included in this study. The study participants belonged to reproductive age group between 18- 45 years.

Women having history of twin pregnancies, multiple pregnancies, renal diseases, liver diseases, cardiovascular diseases, severe anemia, diabetes mellitus, patients receiving antihypertensive and other hypertensive disorders of pregnancy were excluded.

2.1 Sample Collection and Analysis

2 ml of venous blood collected from each participant was dispensed into plain container, allowed to clot and the serum was separated, stored frozen at -20º till further analysis. Serum trace elements copper and zinc were analyzed at SAIF (Sophisticated Analytical Instrument Facility) Department, IIT Bombay by Inductively Coupled Plasma atomic Emission spectrometer, Model ARCOS from M/S Spectro, Germany) (ICP-AES) technique. Serum was pre-digested by taking 1 ml of serum and appropriately diluted with 0.5 ml HNO_3, 0.5 ml perchloric acid and 5 ml distilled water. Serum samples were filtered prior to the analysis. Prepared sample were stored at refrigerator (stable for 8 days at -20°C). Absorbances were read at 324.7 and 213.8 nm for copper and zinc respectively in ICP-AES. The concentrations of copper and zinc in serum were expressed in µg/dl [10]. It is more sensitive technique and it has multielements detection capability.

3. RESULTS

Mean age and gestational age in the preeclamptic cases and normal pregnant controls were not significantly different. But both systolic blood pressure (SBP) and diastolic blood pressure (DBP) were significantly higher for the preeclamptic group than normal pregnant women (Table 1). Since this study was conducted in Rural Health Care Centre, 80% patients were belonged to lower socioeconomic status and rest 20% were middle class patients. The serum levels of total copper was significantly higher ($p<0.001$) in preeclamptic patients when compared to normal pregnant women, while serum total zinc was non significantly lower in preeclampsia as compared to normal pregnant women ($p>0.05$) (Table 2).

3.1 Statistical Analysis

All values were expressed as mean ± SD. Z test was used to compare the means of the groups for serum copper and zinc. Kolmogorov-Smirnov test was performed to assess whether data satisfies assumptions of normality. If p was greater (>) than 0.1, it was concluded that data follows normal distribution. However, for all study parameters p found > 0.1. Hence the parametric tests were applicable to analyze the data.Data was analyzed using SPSS software (version 17 for window).

4. DISCUSSION

Preeclampsia is a multifactorial and multisystem disorder with no individual factor to account for causing it [11]. Copper is an essential co-factor of antioxidant enzyme superoxide dismutase (SOD) and ceruloplasmin. Absorption of copper occurs from enterocytes of the duodenum and small intestine. This gets incorporated in the liver to form ceruloplasmin. Ceruloplasmin is circulating copper binding protein and excess is excreted into bile. Copper is involved in multiple enzymatic reactions with diverse physiological roles from melanin production to wound healing and electron transport. It stimulates the absorption of iron and is required for the synthesis and function of hemoglobin [12,13,14]. Zinc is involved in more than 300 different enzymes and acts as an signalling molecule which is able to communicate between cells by converting extracellular stimuli to intracellular signals and controlling intracellular actions. Zinc plays a substantial role in enhancing reproductive health [15,14].

The results of present study revealed significant rise in serum total copper in preeclampsia as compared to normal pregnant women (213.13 ± 38.6 vs 196.2 ± 25.9 in µg/dl, Gr II Vs Gr I, $P<0.006$), (Table 2). Literature revealed higher serum copper was associated with an increased risk of preeclampsia [16]. Yuqin Fan et al observed that serum copper in preeclamptic patients was significantly higher than that of healthy pregnant women [17].

During pregnancy, serum copper concentration increases owing to induction of ceruloplasmin by estrogen, returning to normal non pregnant values after delivery [8,18]. Both copper and ceruloplasmin levels increase with the period of gestation and it was significantly higher during2nd and 3rd trimester of pregnancy. The maximum increase was observed during 3rd trimester of

Table 1. Comparison of demographic parameters in study groups

Parameters	Normal pregnant women (Group I) (Mean ± SD) (n=60)	Overall preeclamptic women(Group II) (Mean ± SD) (n=60)	Z values	p values
Age (years)	23.80 ± 3.37	22.93 ± 3.57	1.36	0.17#
Gestational Age (Weeks)	32.05 ± 4.0	30.92 ± 4.24	1.51	0.14#
Systolic blood pressure (mmHg)	116.50± 4.07	151.30 ± 3.57	7.2	<0.001**
Diastolic blood pressure (mmHg)	76.93 ± 4.5	98.93 ± 10.9	6.69	<0.001**

*# p>0.05- non- significant,*p<0.05, **p<0.001*

Table 2. Comparison of serum copper and serum zinc in study groups

Parameters	Normal pregnant women (Group I) (Mean ± SD) (n=60)	Preeclamptic women (Group II) (Mean ± SD) (n=60)	Z values	p values
Copper (µg/dl)	196.20 ± 25.9	213.13 ± 38.6	2.82	0.006**
Zinc (µg/dl)	77.15 ± 14.5	76.23 ± 13.13	0.36	0.72#

*# p>0.05- non significant,*p<0.05, **p<0.001*

pregnancy which may be due to increased ceruloplasmin [19]. The biochemical role of copper is to assist in catalysis. Ceruloplasmin is known as an acute phase reactant and predominant copper binding protein having antioxidant function. It has ferroxidase properties that catalyses the conversion of ferric ion to ferrous form. Deficiency in ceruloplasmin leads to cellular iron accumulation supporting its ferroxidase role [20,18].

Maintenance of adequate serum copper may be desirable. Significantly higher serum copper was observed in the preeclamptic women in this study. Contradictory to the above study low level of serum copper was mentioned by Gayathri B and Lewandowska M et al. [21,22] and no significant change in serum copper and serum zinc were reported by FZ Muna et al. in preeclampsia [23]. In preeclampsia, it is presumed that mobilization of copper from maternal tissue, especially from damaged liver occurs due to vasoconstriction which may be responsible for raised serum copper. This may be due to decreased biliary excretion induced by hormonal changes typical during pregnancy [23] [8]. The modest elevation in copper may enhance the production of free radicals and contribute to oxidative stress [23]. Copper and iron are redox-active transition metals and can participate in single electron reactions. High levels of maternal free copper catalyse formation of undesirable hydroxyl radicals via Fenton-like reactions [24,25,26]. These free radicals are thought to be involved in many physiological and pathological processes and are known to oxidatively modify DNA, lipids and proteins [24,23]. Exposure to trace elements such as, copper and iron may also leads to molecular and endothelial cell damages [25,27]. This finding was supported by Derouiche Samir [27].

Previous studies had shown that during pregnancy, ATP7B plays a role in transporting copper from the placenta to maternal circulation, thus preventing fetal overload. Another reason for the increase copper in preeclampsia is due to blockade in the transfer of copper to fetus by the placenta [26,28,29]. If dysfunctional, excess copper remains in the fetus and placenta leading to oxidative damage resulting in fetal loss or may leads to oxidative damage [12,30]. Hence, high levels of maternal serum copper could be dangerous for the fetus may cause cerebral disorder and it may induce abortion in the mother [13].

In this study non-significant low levels of serum zinc was observed in preeclampsia as compared to normal pregnant group (76.23 ± 13.1 vs 77.15 ± 14.5 µg/dl, Gr II Vs Gr I, P>0.72), (Table 2). Zinc is an essential component of antioxidant enzyme SOD. Zn may function as an antioxidant by two mechanisms. It can increase iron and copper availabilities by competing for their binding proteins. Moreover, Zinc binds the sulfhydryl groups in proteins, protecting them from oxidative damage [25]. There is progressive decline in the level of serum zinc from Ist trimester to the 3rd trimester in both normal and the preeclamptic women [31]. During pregnancy progressive hypozincemia might be attributed possibly due to hypoalbuminemia resulting from albuminuria, increased transfer of zinc from

mother to the fetus, due to increase plasma volume expansion, enhanced endogenous steroid production and increased urinary excretion and low dietary bioavailability [32,8]. But in present study, non-significant low levels of zinc was observed which was in accordance with lou Golmohammad [33]. Significant reduced serum zinc was reported by Deepa Kanagal [34].

5. CONCLUSION

Present study postulate that elevated serum copper is involved in free radicals production. Therefore it may be one of the important related factors in the etiopathogenesis of preeclampsia. This study postulate estimation of serum copper may help the clinicians in early diagnosis of preeclampsia, hence minimizing complications in both mother and fetus. If, optimal serum copper is maintained during antenatal period, it may reduce the severity of preeclampsia as well. However to prove whether it is cause or effect more detailed study of copper metabolism that is serum total copper, urinary copper and serum ceruloplasmin may needed on a large sample size.

DISCLAIMER

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CONSENT AND ETHICAL APPROVAL

The study was approved by the Institutional Ethics Committee of MIMER Medical College, Talegaon Dabhade, Pune. A written informed consent was taken from the each participant prior to sample collection.

All authors hereby declared that all experiments have been examined and been performed in accordance with the ethical standards.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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