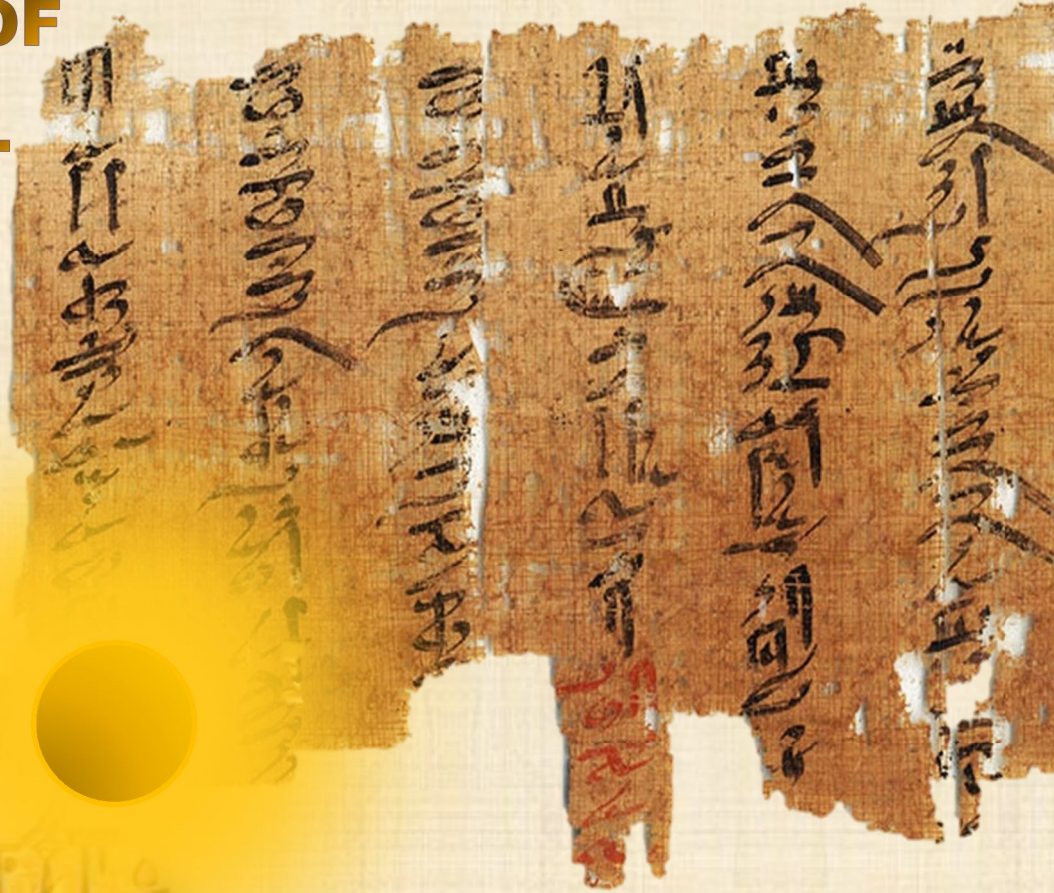


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Original article

Selected Trace Elements in Egyptian Females with Preeclampsia

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ABSTRACT

Background: Evidence exist indicating that, trace elements could play a role in preeclampsia [PE]. However, controversy exist regarding the role of the value of trace elements supplementation on the pregnancy outcome.

Aim of the work: To estimate serum levels of some trace elements [selenium, calcium, magnesium, iron and zinc] in females developed preeclampsia and compare them to healthy pregnant females and correlate it with pregnancy outcome.

Patients and Methods: 140 females were included in each group [preeclampsia and controls]. All had been assessed clinically, and by laboratory and ultrasound investigations. In addition, serum levels of selenium, calcium, magnesium, iron and zinc, had been determined and correlated with pregnancy outcome.

Results: There was statistically significant increase of all trace elements in preeclamptic when compared to control groups. There was significant increase of females with deficient zinc, iron, calcium, magnesium and selenium in PE when compared to control group [83.6%, 19.3%, 30.7%, 27.9% and 40.0% vs 22.9%, 5.7%, 4.3%, 2.9% and 5.0% respectively]. The odds ratio where higher for zinc, followed by selenium, magnesium, calcium and finally iron deficiency. In addition, zinc, iron, calcium, magnesium and selenium were inversely and significantly correlated with systolic blood pressure. Preeclampsia was associated with worse maternal-fetal outcome when compared to controls.

Conclusion: Lower levels of studied trace elements are associated with development of preeclampsia and we assume that, supplementation by such elements could reduce the risk of preeclampsia. However, this assumption needs to confirmed in future trials.

Keywords: Preeclampsia; Iron; Zinc; Selenium; Calcium.

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* Main subject and any subcategories have been classified according to research topic.

INTRODUCTION

Preeclampsia [PE] is an exclusive disorder of human pregnancy and it usually associated with increased perinatal morbidity and mortality. Globally, it affects up to 10% of all pregnancies^[1]. It specifically affects females in developing countries ^[2]. PE can exert harmful effects on the mother herself, her fetus and neonate^[3]. The diagnosis of PE is confirmed by increased blood pressure [systolic pressure above 140 mmHg and diastolic pressure above 90 mmHg] with proteinuria [more than 300mg/24 hours], platelet aggregation, lower limb edema in the second half of pregnancy or exceptionally, immediately after delivery^[4]. PE is called the disease of theories, as its cause still uncertain. The cardinal manifestation of PE is hypertension, and in complicated cases, there are manifestation of multiple organ dysfunction^[5].

PE incidences in developing countries extends between 20 and 80% with high maternal mortality and an incidence rate of 15% preterm births. This high incidence led researchers to suggest a role of nutritional elements in PE and researchers had been focused on different nutrients especially trace elements, and **Elind**^[6] speculated that, trace elements [TE] may share to an endothelial tissue dysfunction, the main proposed pathophysiological mechanism of PE development^[7].

Many authors explained the role of trace elements by as an essential elements in the normal functions of the cell, as structural component, enzyme cofactors and redox sensors^[5]. However, controversy exist regarding role of trace elements in PE. Some authors documented changes in serum levels of trace elements in pre-eclampsia^[8-9], and other did not find any association^[10]. However, the importance of adequate supply of minerals and micronutrients to pregnant women and its beneficial effects for both the mother and her fetus is not challenged. This led to fortify pregnant mother with vitamins and trace elements. This reflects its important role and again raise the research about its role in

pathogenesis of complicated pregnancies by PE^[11-12].

In addition, previous reports indicated the link between low calcium and risk of PE^[13-14], which had not been confirmed by others^[15]. Similarly, reduced antioxidant nutrients, such as zinc, iron, and selenium, had been reported to have a role in PE ^[16], which could not be confirmed by randomized controlled trials [RCTs], revealed development of PE irrespective of supplementation by trace elements^[17]. Thus, research in those elements is of crucial importance for physicians and health planners, and as preeclampsia and eclampsia is a significant health problem, elucidating the potential role of trace elements in PE development and prevention is of paramount importance.

AIM OF THE WORK

The present clinical trial was designed to estimate the serum levels of selenium, calcium, magnesium, iron and zinc in females developed PE and compare the results with normal health controls. In addition, all females will be followed till the end of their pregnancy to document their outcome.

PATIENTS AND METHODS

This is a prospective comparative study carried out at Al-Azhar university hospitals [Al-Hussein and Damietta University Hospitals], during the period extending from January 2019 to March 2020. For estimation of a justified sample of populations we used the following formula: sample size = $Z_{1-\alpha/2}^2 p[1-p]/d^2$, where $Z_{1-\alpha/2}$ is the standard normal variation [and at 5% type 1 error, it is 1.96], P is expected proportion in population based on previous studies, and d is the absolute error or precision; and based on this equation and prevalence rate of 10.0%, absolute error of 5% and precision of 95.0%; a 138 patients were needed. Thus, in each group we included 140 females in each group [preeclamptic group and control group]. Females who developed PE were in their second half of pregnancy [mainly third

trimester, with a singleton pregnancy]. Females with one or more of the following had been excluded from the study: history of hypertension and/or proteinuria before pregnancy or during the first half of their pregnancy, obesity, any associated chronic medical disease, twin pregnancy, abruptio placentae, coagulation disorder, convulsions, and mineral and trace nutrients supplementation during the last year before conception. Preeclampsia was recognized [confirmed] when one measurement of diastolic blood pressure was ≥ 110 mmHg, or two measurements with 6 hours apart were ≥ 90.0 mmHg, but lower than 110 mmHg; with urinary proteinuria [at least +1 with dipstick reagent strip; 300 mg/24 hours]^[4].

Females in control group were normotensive, without other known risk factors.

Ethical considerations: All participating females in the study had been signed an informed consent after full clarification of the study. Their rights were preserved and assurance about confidentiality was expressed. In addition, the study protocol was approved by the local research and ethics committee of our institutions.

All females assessed clinically after full history taking and essential lab investigations [complete blood count, liver and kidney function tests, electrolytes, trace metals and protein in urine] had been carried out. In addition, abdominal ultrasound had been carried out to document the gestational age, and uterine artery doppler had been done. Then females were followed up to their delivery, and their pregnancy outcome had been documented.

For estimation of studied elements, the blood samples had been drawn on EDTA in the last week before delivery, plasma had been separated by centrifugation and then kept at -20° till the time of assessment of selenium, calcium, iron, magnesium and zinc. The samples then had been transferred to a specific lab of faculty of science to measure trace elements by an atomic absorption spectrophotometer [SOLAAR, Atomic

Absorption Spectrophotometer, Thermo Electron, Cambridge, UK]^[18].

Statistical data analysis: documented data had been coded and fed to a software computer package [the Statistical package for social science [SPSS] program], version 21 for windows [IBM® Inc., Chicago, IL, USA]. Data had been presented as mean, standard deviation, frequency and percent distribution according to the type of data. Comparison between groups had been carried out by independent samples student [t] test for numerical data and Chi square [χ^2] for categorical data. Bivariate correlation was estimated by calculation of Pearson's correlation coefficient [r] which determines the power and direction of correlation. *p* values less than 0.05 was considered statistically significant.

RESULTS

Patient characteristics were presented in table [1]. Both study [PE] and control groups were comparable as regard to patient age, gravidity and gestational age at the diagnosis of PE. However, parity was significantly decreased among PE when compared to control groups [1.57 ± 0.55 vs 1.77 ± 0.51 respectively]. In addition, both systolic and diastolic blood pressure were significantly increased in PE group.

Table [2] described the results of Lab investigations; the red cell count, hemoglobin and platelets were significantly decreased among PE when compared to control groups, while creatinine, total bilirubin, SGPT, SGOT and uterine artery RI were significantly increased among PE group. However, no significant difference was reported between both groups regarding white cell count and serum urea.

Table [3] represented the levels of studied trace elements; zinc levels ranged between 39 and 106 $\mu\text{g/dl}$, while iron ranged between 50 to 156 $\mu\text{g/dl}$. In addition, calcium ranged between 7.10 and 11.80 mg/dl, while magnesium ranged between 1.40 to 2.64 mg/dl. Finally, selenium ranged between 56 to 108 ng/ml. there was

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statistically significant decrease of all studied elements in PE when compared to control group.

For better reflection of the association between studied elements and PE development, data were transformed to qualitative form and percentage of females with low or deficient values had been determined. Interestingly, there was statistically significant increase of females with deficient zinc, iron, calcium, magnesium and selenium in PE when compared to control group [83.6%, 19.3%, 30.7%, 27.9% and 40.0% vs 22.9%, 5.7%, 4.3%, 2.9% and 5.0% respectively]. The odds ratio where higher for zinc, followed by selenium, magnesium, calcium and finally iron deficiency [Table 4].

Regarding pregnancy outcome, there was significant decrease of GA at delivery, increased

CS mode of delivery, reduced neonatal weight, and APGAR score at first and fifth minutes in PE when compared to control group [Table 5].

In the present work, each of zinc, iron, calcium, magnesium and selenium were inversely and significantly correlated with systolic blood pressure. The powerful correlation was between zinc and systolic blood pressure. In addition, each of zinc and iron were inversely and significantly correlated with diastolic blood pressure and significant correlation was between zinc and diastolic BP. Finally, there was significant, proportional [positive] correlation between each of iron, calcium and magnesium with neonatal APGAR score at fifth minute, and between selenium and the RBCS [Table 6].

Table [1]: Patient characteristics among studied populations

Variables	PE group	Control group	Test	P value
Patient age [years]	29.05±3.90	28.35±3.86	1.49	0.14
Parity	1.57±0.55	1.77±0.51	3.02	0.003*
Gravidity	2.75±0.64	2.82±0.52	0.92	0.36
GA at diagnosis	31.88±1.48	32.01±1.47	0.73	0.46
Systolic BP	150.93±6.02	115.93±7.48	43.14	<0.001*
Diastolic BP	98.04±3.58	74.68±8.53	29.87	<0.001*

Table [2]: Lab instigations and RI of uterine artery among studied populations

Parameters	PE group	Control group	Test	P value
RBCs x 10 ⁶ /cell/ml	4.07±0.40	4.19±0.35	2.66	0.008*
Hemoglobin [g/dl]	11.01±1.04	11.27±0.95	2.18	0.030*
WBCs x 10 ³ /cell/ml	8.71±1.09	8.81±0.84	0.85	0.39
Platelets x 10 ³ /cell/ml	248.22±28.11	266.91±39.73	4.53	<0.001*
Urea [mg/dl]	27.04±4.15	27.29±4.34	0.51	0.61
Creatinine [mg/dl]	1.03±0.14	0.98±0.15	2.59	0.010*
Bilirubin [mg/dl]	1.07±0.17	1.04±0.14	2.04	0.043*
SGOT [IU/ml]	28.97±6.76	27.39±5.78	2.09	0.037*
SGPT [IU/ml]	27.75±6.12	25.47±4.79	3.46	0.001*
Uterine artery RI	0.67±0.03	0.55±0.06	23.78	<0.001*

Table [3]: Trace elements among studied females

Variable	PE group	Control group	Test	P value
Serum zinc [µg/dl]	58.94±11.19;39-86	85.92±13.8;60-106	17.96	<0.001*
Iron [µg/dl]	94.12±28.34;50-156	100.84±18.19;50-150	2.35	0.019*
Calcium [mg/dl]	9.14±1.00;7.10-11.30	10.24±0.88;8.0- 11.80	9.79	<0.001*
Magnesium [mg/dl]	1.80±0.17;1.40-2.20	2.07±0.16;1.61-2.40	13.61	<0.001*
Selenium [ng/ml]	72.66±8.23;56-95	83.71±8.89;64-108	10.78	<0.001*

Table [4]: Risk estimate of low values of trace elements for PE development

Variable	PE group	Control group	Odds ratio	95% CI	P value
Zinc deficiency	117[83.6%]	32[22.9%]	4.47	3.05-6.52	<0.001*
Iron deficiency	27[19.3%]	8[5.7%]	1.67	1.33-2.09	<0.001*
Hypocalcemia	43[30.7%]	6[4.3%]	2.09	1.73-2.51	<0.001*
Hypomagnesemia	39[27.9%]	4[2.9%]	2.12	1.78-2.53	<0.001*
Selenium deficiency	56[40.0%]	7[5.0%]	2.29	1.90-2.77	<0.001*

Table [5]: Pregnancy outcome among studied populations

Parameters		PE group	Control group	Test	P value
GA at delivery		36.74±0.57;36-39	38.20±1.07;36-40	14.12	<0.001*
Mode of delivery	NVD	93[66.4%]	124[88.6%]	19.68	<0.001*
	CS	47[33.6%]	16[11.4%]		
Baby gender	Male	72[51.4%]	79[56.4%]	0.70	0.40
	Female	68[48.6%]	61[43.6%]		
Baby weight [kg]		2.7446±0.1246;2.50- 3.20	3.0294±0.2065;2.60-3.42	13.97	<0.001*
APGAR score [1 st]		5.14±0.41;4-6	5.77±0.55;5-7	10.80	<0.001*
APGAR score [5 th]		8.24±0.69;7-9	8.52±0.50;8-9	3.83	<0.001*

Table [6]: Correlation between trace elements and pregnancy outcome among study group

	Zinc	Iron	Calcium	Magnesium	Selenium
Systolic	-0.493**	-0.399**	-0.214*	-0.182*	-0.171*
Diastolic	-0.520**	-0.313**	-0.101	-0.083	-0.082
Fifth Minute APGAR	0.007	0.183*	0.254**	0.253**	0.046
RBCs	0.111	0.159	0.108	0.011	0.169*

*. Correlation is significant at the 0.05 level [2-tailed]; **. Correlation is significant at the 0.01 level [2-tailed]. NB: correlation had been calculated for all studied variables, but only significant correlation was presented in the above table.

DISCUSSION

This study had been performed to estimate the serum calcium, magnesium, iron, zinc and selenium levels in preeclampsia and in normal pregnancy, and to assess the potential association between pregnancy outcome these trace elements. Results revealed significant reduction of studied elements in PE when compared to control group. The risk of PE developed increased with such reductions denoting possible role of trace elements deficiency and development of PE. This was confirmed by significant and inverse correlation

between BP, mainly systolic and level so studied elements. Finally, PE was associated with adverse pregnancy outcome [preterm delivery, low birth weight and low APGAR score]. Magnesium, calcium and iron were correlated with APGAR score, while selenium correlated with RBCs, but such correlations were mild although they were significant.

Previous studies indicating a possible association between low calcium intake or low serum levels and increased risk of PE development are existed^[13-14].

However, **Kant et al.**^[15] questioned these findings as they revealed no association between calcium levels, dietary calcium intake or supplementation during pregnancy and prevention of PE development or reduction of adverse perinatal outcome. However, **Kim et al.**^[19] reported that, they a strong associated between reduced levels of serum calcium and zinc and risk of PE development. They reported significant lower levels of zinc and calcium, as in the current study. However, they reported significant higher serum levels of iron in PE group when compared to control group [the current study contradicts these results]. This could be explained by the higher rate of iron deficiency anemia in the Egyptian society.

Additionally, low iron exerts harmful effects on all body systems, as well as higher iron with different mechanism. The higher iron mainly increased oxidative stress, the mechanism that seems to share in development of PE. It is well known that Fe deficiency is a risk factor for premature delivery, stillbirth and low birth-weight of children^[20-21].

In agreement with the current study, **Kumru et al.**^[22] reported significant reduction of serum zinc level Turkish females with PE than in controls.

In addition, **Jain et al.**^[2] reported significant reduction of serum calcium, zinc and magnesium in Indian PE when compared to healthy females.

Hofmeyr et al.^[23] carried a meta-analysis of randomized controlled trials and conclude that, calcium supplementation [1.5-2g] significantly reduced the risk of PE [RR: 0.48, 95% CI:0.33-0.69].

However, **Villar et al.**^[14] revealed that calcium supplementation [1.5g] for women with low calcium intake was associated with mild, non significant reduction of the risk of PE development.

To explain the association between reduced calcium and PE development, **Kim et al.**^[19] stated that, low calcium may increase blood pressure by

stimulation of parathyroid hormone or rennin release, with subsequent increase of intracellular calcium in smooth muscles of blood vessels and vasoconstriction.

Farzin and Sajadi^[24] also reported significant reduction of serum calcium, zinc and magnesium in PE [as in the current work].

In addition, **Negi et al.**^[25] reported significant reduction of magnesium zinc and copper in the umbilical cord blood of preeclamptic and eclamptic pregnancies.

However, **Elmugabil et al.**^[3] reported significant reduction of serum zinc and calcium but significant elevation of magnesium in PE and calcium and magnesium showed no significant correlation.

Also, **Vafaei et al.**^[26] reported no significant difference between 40 controls, 20 mild and 20 severe preeclamptic Iranian females, regarding levels of calcium, magnesium and zinc.

Magnesium is a very important trace element, as it acts as a cofactor for different enzyme systems^[27]. It is mandatory for tone, contractility, and reactivity of blood vessels; hence, it plays a significant role [as calcium do] in the regulation of blood pressure. This reflects its therapeutic potential in management of PE^[28].

Interesting finding of the current work is the reduction of both calcium and magnesium in PE. This counterpart the competition relation between calcium and magnesium.

Fortunately, a previous report by **Jahnen-Dechent and Ketteler**^[29] had been delineated the competition between magnesium and calcium with one another for binding sites on plasma proteins.

Additionally, it was reported that, the interaction at molecular levels and carrier proteins should be considered when the level of calcium, magnesium and albumin are investigated^[30]. Moreover, trials have shown that magnesium counteracts calcium-dependent release of

acetylcholine at motor endplates^[29]. Thus, magnesium may be regarded as a natural calcium antagonist^[2]. Most importantly, the balance between calcium and magnesium is crucial for blood pressure regulations, with vasoconstrictive effect of calcium and vasodilatory action of magnesium^[13].

Zinc is an essential element for carbohydrate, protein and nucleic acid metabolism. In addition, it had a role as antioxidant, in cell division and differentiation. Thus, it essential for embryogenesis. Interestingly, zinc requirements are doubled as normal non-pregnant females during the third trimester^[31-32].

Zinc deficiency in PE may result from hemodilution caused by fluid retention, endogenous steroid production and fetal uptake of zinc from her mother circulation. It may also be due to reduced levels of zinc binding protein^[33].

In a meta-analysis, **Ma Y et al.**^[34] concluded that, there was significant reduction of serum zinc in PE than healthy controls. They added, a moderate zinc supplementation during pregnancy is recommended to reduce the incidence of PE.

In the current work, selenium was significantly reduced in preeclamptic females. This may be due to excessive consumption of Se for scavenging reactive oxygen radicals and protected effect exerted to protect foetus against damage caused by reactive oxygen radicals^[16].

In the present work, both groups were comparable as regard to patient age and gestational age. These results are comparable to those reported by **Muna et al.**^[33] and others^[35-36].

In the present work, complete blood count examination revealed lower levels of RBCs, hemoglobin and platelets in PE group.

Makuyana et al.^[37] reported no significant changes in hematological parameters [hemoglobin, WBC, red blood cell and platelet count] in 38 preeclamptic and 72 normal women.

Tesfay et al.^[38] have reported significant reduction of platelet counts and platelet volume among pre-eclamptic females when compared with healthy controls. They added, platelet count and volume could be used as a rapid test for prediction of preeclampsia.

The strength of the current study is the justified sample of patients included. However, one limiting step of the current work is that it did not take into consideration the probable interaction between measured elements and their carrying proteins [e.g. albumin], and pH changes which could affect the serum levels. Thus, in future studies it is advisable to be considered.

In short, we could conclude that, reduced levels of studied trace elements are associated with PE development. Theoretically, the supplementation by such elements could reduce the risk of PE. However, the scope of the current work was beyond examination of the effect of complementation on PE risk. Future studies are recommended to examine the role of complementation by such trace elements on the risk of PE development.

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None.

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