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Original Article

Correlation between serum Ca, Mg, Zn & Cu and hypertension in pre-eclampsia

Mahmoud K. Zaater

Radiation Health Research Dept. National Center for Radiation Research and Technology, Atomic Energy Authority, Cairo, Egypt

Abstract

Pre-eclampsia is potentially preventable, but potentially morbid and/or a fatal disease. The aim of this work is to study serum levels of copper, zinc, calcium and magnesium in pregnant patients with pre-eclampsia. 15 patients diagnosed as pre-eclampsia "patient group" (group 1) and two age matched control groups [8 essential hypertension non pregnant women (group 2)] and [8 normotensive pregnant women (group3)] were studied. All persons were subjected to full history with special attention to past history of hypertension and renal disease, clinical examination, routine laboratory investigation and estimation of serum levels of copper, zinc, calcium and magnesium by spectrophotometer method. The results revealed significant increase of serum uric acid in group1 (6.64±0.62 mg%) vs. (3±0.55 mg%) in group2 and (4.12±0.5 mg%) in group3, significant reduction in serum calcium in group1 (92.32±10.94 µg/dl) vs. group 2&3 (122.9±8.49 µg/dl & 130.92±3.91 µg/dl), significant increase in serum magnesium in group1 (59.9±11.18 µg/dl) vs. group 2&3 (37.71±4.92 µg/dl & 38.71±1.4 µg/dl), significant reduction in Ca/Mg ratio in group1 (1.58±0.33) vs group 2&3 (3.31±0.49 & 3037±0.07), significant increase in serum copper in group1 (4.83±1.49 µg/dl) vs group 2 (2.64±0.42 µg/dl) and group 3 (2.09±0.68 µg/dl) and significant reduction in serum zinc in group 1 (1.47±0.49 µg/dl) vs group 2 (3.15±0.46 µg/dl) & group 3 (3.94±1.52 µg/dl). The significance and pathogenic mechanisms of these abnormalities are explained.

Key words: Pre-eclampsia, calcium, magnesium, zinc, copper, uric acid

Correspondence and offprint requests to: Dr. Mahmoud K. Zaater, MD, Radiation Health Research Dept. National Center for Radiation Research and Technology, Atomic Energy Authority. Cairo, Egypt.

Introduction

Pre-eclampsia is a pregnancy specific disease, it is defined as the onset of hypertension with proteinuria, edema, or both, at greater than 20 weeks gestational age. Hypertension is defined as a rise in systolic blood pressure of greater than 30 mmHg or diastolic blood pressure greater than 15 mmHg or blood pressure greater than 140/90mmHg on more than two occasion 6 hours apart. Transient gestational hypertension is the development of hypertension during pregnancy without other signs of pre-eclampsia, [1]. Hypertension is the defining manifestation of pre-eclampsia. Women who have higher blood pressure in the first trimester of pregnancy have a greater risk of developing overt pre-eclampsia at the end of pregnancy. 32% of women with a mean arterial pressure greater than 90 mmHg in the second trimester will develop pre-eclampsia compared with only 2% of those with a mean arterial pressure less than 90 mmHg [2].

Hypertension is a consequence of systemic vasoconstriction secondary to endothelial dysfunction. Women with pre-eclampsia are less sensitive to endothelial factors producing vasodilatation as prostacyclin and nitric oxide, showing an increased vascular sensitivity to infused angiotensin II before they develop overt hypertension [1]. Manifestations of coagulopathy as thrombocytopenia, microangiopathic hemolytic anemia, fibrin deposition in the kidney and liver, and consumptive coagulopathy also occur in pre-eclmpsia. Uric acid clearance falls often before the rise in the serum creatinine. Serum uric acid is usually diminished in normal pregnancy. A serum urate more than 5.5 mg/dl strongly suggest pre-eclampsia. Urinary excretion of calcium is reduced in pre-eclampsia [1].

Pre-eclampsia is triggered by a congenital or acquired defect of placentation resulting in abnormal uterine spiral arteries remodeling and consequent fetoplacental ischemia, then uncharacterized factors released into the

circulation by the ischemic fetoplacental unit would trigger endothelial dysfunction with consequent vascular hyperactivity, proteinuria, and platelet activation [3]. Arterial tone and water & electrolyte homeostasis are regulated by several peptides including angiotensin II, bradykinin, atrial naturitic peptide and endothelins. The metabolism of these peptide is essentially controlled by three enzymes (angiotensin converting enzyme, endopeptidase and endothelin converting enzyme) which all belong to a group of zinc metallopeptide [4].

Aim of the study

Our aim is to study the relation between serum Copper, Zinc, Calcium and Magnesium and the occurrence of hypertension and pre-eclampsia in pregnant women.

Material and methods

The study includes three groups:
1st group: 15 patients diagnosed as pre-eclampsia (table 1).
2nd group: 8 patients (women) diagnosed as essential hypertension (non pregnant) with age matched with the 1st group.
3rd group: 8 normal pregnant women (non hypertensive) as control group, their age are matched with both other groups.

Table 1. Patients with pre-eclampsia

Pt. No	*Blood P.*	*Mean bl.P*	*U.Protein*	*L.L.edema*
1	140/100	113.32	++	++
2	150/95	113.33	+++	++
3	150/100	116.66	++	++
4	140/90	106.66	++	++
5	145/100	114.99	++	++
6	150/90	110	++	+++
7	150/90	110	+++	++
8	150/95	113.33	+++	++
9	140/90	113.32	++	+++
1	160/90	113.33	+++	+++
11	145/90	108.33	++	++
12	140/90	108.33	++	++
13	150/95	110	+++	++
14	150/90	110	+++	++
15	140/90	113.32	++	++

All persons in the study were subjected to the following:

- Full history with special attention to past history of hypertension and renal disease.
- Clinical examination.
- Complete blood picture.
- Urine analysis.
- Urinary protein.
- Serum uric acid. Serum creatinine
- Estimation of serum levels of the following element using atomic absorption ion spectrophotometer method: Copper, Zinc, Calcium and Magnesium.

Atomic Absorption Ion Spectrophotometer method, used in the estimation, is based on the fact that atoms of an element in the ground or unexcited state will adsorb light of the same wavelength that they emit in the excited state. The wavelengths of that light or the resonance lines are characteristic for each element. Atomic absorption spectrophotometer involves the measurement of the light absorbed by atoms in the ground state. Most elements have several resonance lines but usually one line is considerably stronger than the others. The wavelength of this line is generally the one selected for measurement. Occasionally, it may be necessary to select another resonance line either to reduce sensitivity or because a resonance line of an interfering element is very close to the one of interest [5].

Results

Table 2. Represents the results of pre-eclampsia patients

Ca/Mg	*S.Cr mg%*	*S.Ur.A mg%*	*Mg µg/ml*	*Zn µg/ml*	*Ca µg/ml*	*Cu µg/ml*
1.59	0.9	5.9	64.37	1.493	102.2	6.269
1.66	1	7	59.79	1.864	99.34	5.367
2.09	1	6.3	48.2	1.356	101	5.58
1.64	0.95	7.2	52.57	0.922	86.4	5.367

	1.72	0.8	6.8	53	1.344	91.3	5.206
	1.4	0.96	7.1	61.23	2.316	89.2	2.99
	1.51	0.95	5.8	56.47	1.179	85.81	3.114
	0.99	1.1	5.8	73.81	0.978	72.86	4.355
	1.17	1.2	6.2	67.62	0.934	79.07	8.768
	1.25	1.05	6.8	91.49	1.754	114.3	4.026
	1.51	0.9	7.5	54.1	1.305	81.38	2.837
	2.07	0.85	6	48.85	1.35	101.2	4.035
	1.73	0.9	7.4	54.69	0.968	94.85	3.593
	2.18	0.8	7.6	47.73	2.641	104	5.851
	1.27	0.95	6.2	64.58	1.773	81.94	5.234
Mean	1.585	0.954	6.64	59.9	1.478	92.32	4.839
SD	0.33	0.10	0.62	11.18	0.49	10.94	1.49

Table 3. Represents the results of pregnant non hypertensive patients

	CA/Mg	*S.Cr mg%*	*S,Ur.Amg%*	*Mg µg/ml*	*Zn µg/ml*	*Ca µg/ml*	*Cu µg/ml*
	2.6	0.9	2.7	44.76	5.977	116.4	1.892
	2.95	0.8	3.4	37.13	3.993	109.7	1.753
	3.6	0.75	2.1	35.57	2.765	128.4	1.942
	3.75	0.82	3.1	33.7	2.369	126.5	1.717
	2.81	0.99	2.9	42.43	4.147	119.2	2.898
	3.59	0.91	3.5	38.65	2.958	138.6	2.83
	4.13	0.85	3.9	28.3	2.614	116.9	2.88
	3.1	0.8	2.4	41.16	6.75	127.6	0.818
Mean	3.316	0.853	3	37.71	3.947	122.9	2.091
SD	0.494	0.072	0.559	4.928	1.527	8.5	0.685

Table 4. Represents the results of hypertensive non pregnant patients

	Ca/Mg	*S.Cr mg%*	*S.Ur.A mg%*	*Mg µg/dl*	*Zn µg/dl*	*Ca µg/dl*	*Cu µg/dl*
	3.32	0.9	4.3	37.9	3.46	125.9	1.95
	3.45	1.1	4.7	39.29	3.53	132.5	2.03
	3.4	1.2	5.1	40.01	2.43	136.4	2.59
	3.39	0.9	3.7	39.55	3.61	134.2	2.85
	3.29	1	3.8	40.06	2.5	131.8	3.05
	3.3	1.1	4	39.13	2.99	129.4	2.59
	3.52	0.9	3.9	35.41	3.67	124.7	3.15
	3.3	1.1	3.5	38.35	3.01	126.9	2.98
Mean	3.37	1.02	4.12	38.71	3.15	130.22	2.64
SD	0.07	0.10	0.50	1.43	0.46	3.91	0.42

Serum uric acid

There is a significant increase of serum uric acid in pre-eclampsia group (6.64±0.62 mg%) vs. (3±0.55 mg%) in pregnant non hypertensive group and (4.12±0.5 mg%) in non pregnant hypertensive group.

Serum calcium

There is a significant reduction in total "but with the physiologic level" of serum calcium in pre-eclampsia group (92.32±10.94 µg/dl) vs. the other two groups (122.9±8.49 µg/dl & 130.92±3.91 µg/dl).

Serum magnesium

There is a significant increase in serum magnesium in pre-eclampsia group (59.9±11.18 µg/dl) vs. the other two groups (37.71±4.92 µg/dl & 38.71±1.4 µg/dl).

Calcium /magnesium ratio

There is a significant reduction in Ca/Mg ratio in pre-eclampsia group (1.58±0.33) vs. other two groups (3.31±0.49 & 3037±0.07).

Serum creatinine

There is no significant difference in serum creatinine between the three studded groups (0.95±0.1 mg/dl in pre-eclampsia, 0.85±0.07 mg/dl in non hypertensive pregnant and 1.02±0.1 mg/dl in hypertensive non pregnant group).

Serum copper

There is a significant increase in serum copper in pre-eclampsia group (4.83±1.49 µg/dl) vs. pregnant non

hypertensive group (2.09±0.68 µg/dl) and non pregnant hypertensive group (2.64±0.42 µg/dl).

Serum zinc

There is a significant reduction in serum zinc in pre-eclampsia group (1.47±0.49 µg/dl) vs. the pregnant non hypertensive group (3.94±1.52 µg/dl) and the non pregnant hypertensive group (3.15±0.46 µg/dl).

Discussion

The pre-eclampsia group has significantly higher mean serum uric acid levels (6.64±0.02 mg/dl) compared to the other two groups. This is going with the previous result of [3] who use value of >5.5 mg/dl as a diagnostic marker of pre-eclampsia.

Our patients with pre-eclampsia had a lower total mean serum calcium level (92.32±1.94 µg/dl) vs. (122.91±8.49 & 130.22±3.91 µg/dl) in pregnant non hypertensive group and non pregnant hypertensive groups respectively (P<0.05), which could be explained by the low serum albumin level in pre-eclampsia group, secondary to albuminuria and liver affection in pre-eclampsia [6]. Hemo- dilution which is more marked in pre-eclampsia may contribute to the hypocalcaemia observed in the studied group of patients with pre-eclampsia. Serum magnesium can compete with calcium for binding site on protein and membrane and stimulate calcium sequestration by the sarcoplasmic reticulum [7] it may be a cause for increase calcium sequestration and low serum total calcium in our pre-eclampsia patients (73.71±4.92 vs 38.71±1.43 & 37.71±4.72) (P0.05). The elevation of serum magnesium in the studied pre-eclampsia group compared to the non pregnant hypertensive patients and pregnant non hypertensive patients is an evidence supporting this hypothesis.

Rising extracellular magnesium concentration stimulate renin secretion, high concentration of magnesium hyperpolarize cell membrane and inhibit net calcium influx, but, increased calcium and depolarization inhibit the stimulatory effect of high magnesium on renin [8]. Renin cleaves a decapeptide "angiotensin I" from angiotensinogen. The half life of renin is 90 minute and the primary site of renin metabolism is the liver [8]. Angiotensin I is converted to angiotensin II which is a potent vasoconstrictor and patients with pre-eclampsia are hypersensitive to the action of angiotensin II [2].

Our results revealed that the Ca/Mg ratio was 1.58±0.32 in pre-eclampsia group which is significantly higher than to the ratio in the other two groups, non pregnant hypertensive group (3.37±0.07) and pregnant non hypertensive group (3.31±0.49), (P<0.05).

Zinc is important for fetal growth. Several important enzymes require zinc for their activity e.g. thymidine kinase and various RNA & DNA polymerases [9]. Our study revealed a significant decrease in the mean serum zinc level in patient with pre-eclampsia (1.47+0.49 µg/dl) vs. the other two controlled groups, hypertensive non pregnant group (3.15+0.46 µg/dl), and pregnant non hypertensive (3.94+1.52 µg/dl), (P<0.05). This is going with the results reported by [10,11,12].

Low consumption of dietary zinc was reported to be associated with low serum zinc level and increase prevalence of hypertension [13]. Arterial tone and water electrolyte homeostasis are regulated by several peptides including angiotensin II, bradykinin, atrial naturitic peptide and endothelins. The metabolism of these peptide is essentially controlled by three enzymes (angiotensin converting enzyme, endopeptidase and endothelin converting enzyme) which all belong to a group of zinc metallopeptide [4]. High protein food such as meat, fish, and dairy products, are good sources of available zinc. The bioavailability of zinc from vegetables and cereal grains is reduced because phytates (inositol phosphates), cellulose, hemicelluloses, and other dietary fibers inhibit zinc absorption [9]. The availability of dietary zinc decreases by high amount of dietary calcium, phosphorous, iron and copper. Diet rich in protein stimulate zinc absorption, whereas diet low in protein have the opposite effect.

Copper is associated with a number of metalloproteins, as, ceruloplasmin, cytochrome C oxidase, superoxide dismutase, dopamine-b-hydroxylase and tyrosnase. The major function of these enzymes is oxidative-reduction reactions [9]. The most known copper-containing enzymes bind and react directly with molecular oxygen. Ceruloplasmin, the major copper-containing protein in the plasma, has a ferroxidases activity that oxidizes ferrous iron to the ferric state prior to its binding by plasma transferrin. Other metal ion particularly zinc & cadmium compete with copper for sulfhydryl-binding site of metallothionein, thus explaining the antagonism of these metals toward copper absorption [9]. Absorbed copper is rapidly transported as copper-albumin or copper-histidine complexes to the liver where it is stored mostly as metallothionein-like cuproproteins. Copper is released from the liver, mainly as ceruloplasmin, a multifunctional cuproprotein that account for over 95 % of the total copper in plasma. Movement of copper within the cell and its incorporations is regulated by both glutathione and metallothionein.

Our study reveled a significant increase in mean serum copper in pre-eclampsia group (4.83±1.49 µg/dl) vs. (2.64±0.42 µg/dl) in non pregnant hyprtensive group, and (2.09±0.68 µg/dl) in pregnant non hypertensive group. Our results going with the results of previous studies by [14,15,16,17]. Mishandling of copper by albumin contributes to oxidative stress in pre-eclampsia. Copper chelators may represent promising mechanism based antioxidants to attenuate oxidative stress in pre-eclampsia [14]. Significant increase in serum ceruloplasmin level in pre-eclampsia compared to normal pregnancies, with loss of ferroxidase activity of ceruloplasmin in pre-eclampsia serum indicating lack of protective antioxidative action was reported by [15].

In conclusion, the present study revealed that pregnant women with pre-eclampsia have significantly higher

mean serum levels of magnesium associated with significantly lower mean serum calcium levels and lower calcium/magnesium ratio than the control groups. The studied pre-eclampsia patients had also significantly lower mean serum zinc levels and significantly higher mean serum copper levels than the control groups. These abnormalities in mineral ions may contribute to the pathogenesis of pre-eclampsia. Further studies are needed to evaluate the effect of correction of these abnormalities on the natural course of pre-eclampsia.

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