Biol Trace Elem Res (2010) 133:162–170
DOI 10.1007/s12011-009-8423-9

The Role of Calcium, Magnesium, and Zinc in Pre-Eclampsia

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Received: 6 February 2009 / Accepted: 2 June 2009 /
Published online: 23 June 2009

Abstract Pre-eclampsia is the most common medical complication of pregnancy associated with increased maternal and infant mortality and morbidity. Its exact etiology is not known, although several evidences indicate that various elements might play an important role in pre-eclampsia. This study was carried out to analyze and to compare the concentration of calcium, magnesium, and zinc in the serum of women with pre-eclampsia and in normal pregnant women. Fifty clinically diagnosed patients with pre-eclampsia (25 with mild and 25 with severe pre-eclampsia) and 50 normal pregnant controls were enrolled in this study. The serum calcium, magnesium, and zinc levels were estimated with an atomic absorption spectrophotometer. The mean serum levels of calcium, magnesium, and zinc in normal pregnant group were 2.45±0.18 mmol/L, 0.79±0.13 mmol/L, and 15.64±2.4 µmol/L, respectively, while in mild pre-eclamptic group, these were 2.12±0.15 mmol/L, 0.67±0.14 mmol/L, and 12.72±1.7 µmol/L, respectively. Serum levels in severe pre-eclamptic group were 1.94±0.09 mmol/L, 0.62±0.11 mmol/L, and 12.04±1.4 µmol/L, respectively. These results indicate that reduction in serum levels of calcium, magnesium, and zinc during pregnancy might be possible contributors in etiology of pre-eclampsia, and supplementation of these elements to diet may be of value to prevent pre-eclampsia.

Keywords Pre-eclampsia · Calcium · Magnesium · Zinc

Introduction

Pre-eclampsia is a progressive, multisystemic disorder characterized by triad of high-blood pressure to the extent of 140/90 mm Hg or more, edema, and proteinuria, developing after 20 weeks of gestation [1]. It is one of the most common medical complications during pregnancy and the leading cause of both maternal and perinatal morbidity and mortality worldwide [2, 3]. It complicates about 7–10% of all pregnancies. Although it has been studied extensively, its specific etiology and pathophysiology remain obscure [4, 5]. Pre-

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eclampsia has been found to have more impact in developing countries where pregnant women have been reported to consume diets with lesser amounts of essential minerals and vitamins [6].

Abundant studies suggest that imbalance of several specific nutrients during pregnancy have deleterious influences. During pregnancy, an inadequate dietary intake might be harmful not only for the mother but also for the growing fetus [7]. The possible role of various nutrient elements like protein, lipids, calcium, magnesium, zinc, and copper have been emphasized in pre-eclampsia [3, 8, 9].

Belizan and Villar [10] have shown the inverse relationship between calcium intake and hypertension during pregnancy. Similar findings were further supported by other studies [11–13]. An association between pre-eclampsia and hypocalciuria [14], lower urine calcium to creatinine ratio [15], and lower dietary milk intake [16] has also been found.

Magnesium, as an essential trace element, acts as an important cofactor for activation of many enzyme systems [17]. Various studies have suggested the significant influence of magnesium on fetal and maternal morbidity both prepartum and postpartum [18]. Magnesium has a significant effect on tone, contractility, and reactivity of blood vessels and, thus, plays a significant role in physiological regulation of blood pressure. It also has a therapeutic role in the treatment of pre-eclampsia [19].

Zinc is a trace element involved in a variety of biochemical pathways to modulate various functions in the body. Alteration in zinc homeostasis might have a devastating effect on pregnancy outcome [20, 21]. Several reports had suggested that zinc deficiency may be associated with increased incidence of pre-eclampsia [22, 23].

The present study was undertaken to assess the serum levels of calcium, magnesium, and zinc in pre-eclamptic women as compared to normal pregnant women to find out the role of these nutrients in etiology of pre-eclampsia.

Materials and Methods

The present study was carried out in the Department of Obstetrics and Gynecology and Pharmacology of S.N. Medical College and Hospital, Agra. Approval for study was obtained from the Institutional Ethics Committee of our hospital and informed consent was taken from all subjects.

Pre-eclampsia was diagnosed as a blood pressure 140/90 mm Hg or more on two or more occasions, taken 6 h apart, and the presence of protein in urine and/or edema.

The patients with any chronic illness, diabetes mellitus or other endocrine disorder, renal disease, hydatiform mole and other secondary causes of hypertension, malignancy, etc., which were likely to affect the serum level of calcium, magnesium, and zinc, were excluded from the study.

Fifty clinically diagnosed patients with pre-eclampsia (25 with mild and 25 with severe pre-eclampsia) aged between 16 and 40 years were randomly selected for the study. Fifty of age-matched normotensive pregnant females served as control.

The enrolled women were divided into three groups:

Control group: included healthy pregnant females who were normotensive with no proteinuria or edema

Mild pre-eclamptic group: included women with diastolic blood pressure less than 100 mm Hg with mild edema or proteinuria of mild type (+).

Severe pre-eclamptic group: included women with diastolic blood pressure more than or equal to 110 mm Hg or more with mild, moderate, to severe edema and proteinuria of moderate to severe degree (++, +++, ++++)

All subjects included in our study were subjected to detailed clinical history, general, systemic, and antenatal examination with routine investigations. The blood samples were collected from the antecubital vein of each pre-eclamptic and from control subjects. Sera were separated by centrifugation and stored at 0–4°C until analysis. The serum calcium, magnesium, and zinc levels were estimated with an atomic absorption spectrophotometer (AAS 400 of ECIL India).

Statistical Analysis

The data from patients and control were analyzed by using one-way ANOVA followed by Dunnett′s test. Data were expressed as the mean ± standard deviation (SD), and p value <0.05 was considered statistically significant.

Results

In our study, the majority of women were in the age group of 21–25 years, with period of gestation between 37 and 41 weeks (Table 1).

Serum Levels in Pre-Eclamptic Groups

The mean ± SD values of serum calcium, magnesium, and zinc levels in each group are presented in Table 2.

1. In the mild pre-eclamptic group, the mean serum levels of elements (mean serum calcium concentration 2.12±0.15 mmol/L vs. control 2.45±0.18 mmol/L ($p<0.05$), mean magnesium concentration 0.67±0.14 mmol/L vs. control 0.79±0.13 mmol/L ($p<0.05$), mean zinc concentration 12.72±1.7 µmol/L vs. control 15.64±2.4 µmol/L ($p<0.05$)) were significantly reduced when compared to control.
2. In the severe pre-eclamptic group, the mean calcium level (1.94±0.09 mmol/L vs. control 2.45±0.18 mmol/L), mean magnesium level (0.62±0.11 mmol/L vs. control

Table 1 Demographic Data of Study Groups

Variables	Control n=50	Mild PE n=25	Severe PE n=25
Age (years)	23.92±3.42	23.04±3.76	22.96±3.81
Gestational age (weeks)	33.62±7.83	34.92±3.54	35.08±3.60
Systolic blood pressure (mm Hg)	119.7±7.56	144.7±5.12	174.5±14.2
Diastolic blood pressure (mm Hg)	73.9±8.92	94.8±3.69	117.6±6.90
Mean blood pressure (mm Hg)	88.6±7.07	111.3±3.64	136.5±7.73

Values are expressed as mean ±SD

Mild PE mild pre-eclamptic group, *Severe PE* severe pre-eclamptic group

Table 2 Mean Serum Levels of Calcium, Magnesium, and Zinc in Study Groups

Variable	Control n=50	Mild PE n=25	Severe PE n=25
Serum calcium (mmol/L)	2.45±0.18	2.12±0.15*	1.94±0.09*,**
Serum magnesium (mmol/L)	0.79±0.13	0.67±0.14*	0.62±0.11*
Serum zinc (μmol/L)	15.64±2.4	12.72±1.7*	12.04±1.4*

Values are expressed as mean ±SD

Mild PE mild pre-eclamptic group, *Severe PE* severe pre-eclamptic group

*$p<0.05$ when compared to control group; **$p<0.05$ when compared to mild pre-eclamptic group

0.79±0.13 mmol/L), and mean zinc level (12.04±1.4 μmol/L vs. control 15.64± 2.4 μmol/L) were also significantly decreased as compared to normal healthy controls.

Although the serum magnesium and zinc levels in severe pre-eclamptic patients were lower than those in mild pre-eclamptic patients, the reductions were not statistically significant between the mild pre-eclamptic group and severe pre-eclamptic groups. However, significant difference was found in serum calcium level between severe and mild pre-eclamptic patients.

Serum Levels at Different Weeks of Gestation

Comparison was also done in serum calcium, magnesium, and zinc levels at different weeks of the gestational period. The serum calcium decreased as the gestational period increased and the decline was statistically significant in all periods of gestation (Table 3).

A gradual decrease in mean serum magnesium level was observed with increasing period of gestation in normotensive women, as well as in pre-eclamptic women. The decline was statistically significant between control and pre-eclamptic groups at all periods of gestation except between 29 and 32 weeks; however, the difference was statistically insignificant between mild pre-eclamptic group and severe pre-eclamptic group at all periods of gestation, except between 29 and 32 weeks of gestation, where it was statistically significant (Table 4).

Table 3 Mean Serum Calcium Levels (mmol/L) in Different Gestation Periods

Period of gestation (weeks)	Serum calcium (mmol/L)		
	Control n=50	Mild PE n=25	Severe PE n=25
≤28	2.70±0.09	2.27±0.04*	2.03±0.05*,**
29–32	2.52±0.06	2.19±0.13*	2.02±0.03*,**
33–36	2.42±0.11	2.10±0.09*	1.97±0.07*,**
≥37	2.30±0.12	2.06±0.19*	1.88±0.08*,**

Values are expressed as mean ±SD

Mild PE mild pre-eclamptic group, *Severe PE* severe pre-eclamptic group

*$p<0.05$ when compared to control group; **$p<0.05$ when compared to mild pre-eclamptic group

Table 4 Mean Serum Magnesium Levels (mmol/L) in Different Gestation Periods

Period of gestation (weeks)	Serum magnesium (mmol/L)		
	Control n=50	Mild PE n=25	Severe PE n=25
≤28	0.96±0.52	0.86±0.52*	0.77±0.03*
29–32	0.86±0.05	0.85±0.07	0.70±0.04*,**
33–36	0.76±0.07	0.69±0.05*	0.67±0.03*
≥37	0.67±0.09	0.53±0.07*	0.54±0.09*

Values are expressed as mean ±SD

Mild PE mild pre-eclamptic group, *Severe PE* severe pre-eclamptic group

*p<0.05 when compared to control group; **p<0.05 when compared to mild pre-eclamptic group

There was a significant fall in mean serum zinc level in pre-eclamptic groups as compared to normal pregnancy with advancement of gestational period. This decline among the pre-eclamptic groups was insignificant during ≤28 weeks and from 33 to ≥37 weeks of gestation (Table 5).

Discussion

In developing countries, nutritional deficiencies of both macro- and micro-nutrients are a common health problem, particularly among the women of reproductive age. The risk is further increased with pregnancy because of increased requirements of various nutrients like zinc, copper, vitamin B_{12}, vitamin C, etc., to satisfy the needs of the growing fetus [1, 24, 25]. These nutrients play an important role in regulation of the developmental process in both humans and animals through various enzymes, transcription factors, and their involvement in signal transduction pathways. The changes in levels of these nutrients during pregnancy could affect pregnancy, delivery, and outcome of pregnancy through alterations in maternal and conceptus metabolism [26].

Pre-eclampsia affects approximately 7–10% of all pregnancies, and rates are much higher in developing countries like India. Despite a large list of theories put forward to

Table 5 Mean Serum Zinc Levels (µmol/L) in Different Gestation Periods

Period of gestation (weeks)	Serum zinc (µmol/L)		
	Control n=50	Mild PE n=25	Severe PE n=25
≤28	19.09±2.2	15.1±0.14*	14.47±0.18*
29–32	16.52±1.2	14.98±0.87*	13.17±0.24*,**
33–36	15.01±1.4	12.82±1.0*	12.47±0.081*
≥37	13.83±1.3	11.29±1.2*	10.98±0.92*

Values are expressed as mean ±SD

Mild PE mild pre-eclamptic group, *Severe PE* severe pre-eclamptic group

*p<0.05 when compared to control group; **p<0.05 when compared to mild pre-eclamptic group

explain the etio-pathogenesis of pre-eclampsia, the exact nature of the etiological factors is not known [4, 5, 27]. Recently, the emphasis has been laid on the role of dietary factors in pathogenesis of pre-eclampsia [2, 9]. Dietary deficiencies of calcium, magnesium, and zinc during pregnancy have been implicated in pre-eclampsia, eclampsia, preterm birth, and intrauterine growth retardation [10, 16, 28–30].

This study was performed to investigate the serum calcium, magnesium, and zinc levels in normal pregnancy, as well as in pregnancy complicated by pre-eclampsia, and to evaluate the potential association between pre-eclampsia and these micronutrients.

Minerals like calcium, magnesium, copper, zinc, selenium, etc., are essential for normal human development and functioning of the body. Calcium is required for many important processes, including neuronal excitability, release of neurotransmitter, muscle contraction, membrane integrity, and blood coagulation [31]. Magnesium and zinc act as essential elements for many metabolic pathways, regulate immune system, and act as cofactors for activation of many enzyme systems including antioxidant enzymes [17, 28]. Magnesium supplementation during pregnancy has been found to decrease incidence of preterm birth and intrauterine growth retardation [7, 8]. Similarly, some trials with zinc supplementation during pregnancy have been shown to improve the immune system of the developing fetus and reduce the incidence of pregnancy-induced hypertension, preterm delivery, and low birth weight [29, 32].

Results from various studies have shown the relationship between the change in levels of these elements in mother's serum and high blood pressure [14, 33–35]. The present study showed that mean serum calcium, magnesium, and zinc levels were significantly reduced in pre-eclamptic group when compared with healthy control group.

During pregnancy, there is a progressive decline in concentration of calcium, magnesium, and zinc in maternal serum possibly due to hemodilution, increased urinary excretion, and increased transfer of these minerals from the mother to the growing fetus [14, 33, 36]. In addition, low dietary intake and accelerated metabolism might be other contributing factors [9, 37].

Several studies have reported a link between low dietary calcium intake with increased incidence of pre-eclampsia, and supplementation of calcium has been found to prevent pre-eclampsia and its related complications [10–13, 38]. In this study, a significant reduction was found in serum calcium levels in pre-eclamptic patients as compared to healthy pregnant women. The difference was also seen with progression of gestation period in all groups. This supports an association between altered calcium metabolism and pre-eclampsia. Our findings in the present study are in concurrence with the observations of Kumru et al. [14], Joshi et al. [34], Sukonpan and Phunpong [35], Kisters et al. [39], and Kosch et al. [40], although an opposite trend has also been reported [41, 42]. Somehow, serum levels of calcium seem to play a part in the development of pre-eclampsia, as it has been seen that a reduction in serum calcium level causes increase in release of parathyroid hormone and renin, which in turn cause increase in intracellular calcium in vascular smooth muscle. This increase in intracellular calcium in vascular smooth muscle causes increased vascular resistance and vasoconstriction, thus leading to rise in blood pressure [13, 35].

Recently, attention has also been drawn towards the role of magnesium and zinc in pre-eclampsia. A number of clinical studies have investigated the plasma or serum levels of magnesium and zinc in both normal pregnancies and pregnancies complicated by pre-eclampsia. However, the data from these studies are not so equivocal. No alteration [2, 14, 37], elevation [43, 44], or reduction [33–35, 39] in plasma or serum magnesium concentration have been demonstrated in pre-eclamptic women. Similarly, no change [37, 45], elevation [46, 47], or decrease [14, 34, 48, 49] in serum or plasma zinc has been reported in pre-eclamptic women as compared to normal pregnant controls.

In the present study, serum magnesium and serum zinc levels in pre-eclamptic women were significantly lower than corresponding values in the control group, which is suggestive of some role of these elements in the rise of blood pressure. The decline in serum magnesium and zinc was seen with advancement of gestational period in both mild and severe pre-eclampsia, and decline was more than in the control counterparts in different gestational ages. Hence, changes in plasma or serum levels of these elements might be relevant to the condition of pre-eclampsia because of their known relationship with blood pressure. There could be other possible explanations for the rise in blood pressure in pre-eclamptic mothers due to deficiency of these elements.

Although calcium alone might play a role in the rise of blood pressure, a proper balance of calcium and magnesium is of vital importance to control blood pressure because blood vessels need calcium to contract, but they also require sufficient magnesium to relax and open up. Thus, magnesium acts as a calcium channel blocker by opposing calcium-dependent arterial constriction and by antagonizing the increase in intracellular calcium concentration leading to vasodilatation [19, 35, 50, 51]. In addition, the decreased levels of magnesium during pregnancy might increase the vasoconstrictor response of a large number of neurohormonal agents including epinephrine nor epinephrine, angiotensin-II, serotonin, acetylcholine, and bradykinin, leading to a rise in blood pressure [52].

Recently, the role of oxidative stress or excessive lipid peroxidation has been implicated in pre-eclampsia. There is an imbalance between antioxidant enzyme activities and prooxidant production [53]. Magnesium and zinc are both required for the proper functioning of enzymes like superoxide dismutase, which is required for scavenging free radicals. Deficient concentrations of these elements during pregnancy may cause impairment of antioxidant potential of cells by decreasing superoxide dismutase activity, as well as increased lipid peroxidation, leading to increase in blood pressure [19, 54, 55].

The limitation of this study was a lack of information regarding the dietary intake and daily consumption of these elements in the food of each woman. However, most of the women enrolled in our study belonged to lower and middle socioeconomic status.

In conclusion, the findings of the present study reveal a significant decrease in serum calcium, magnesium, and zinc levels in both mild and severe pre-eclampsia as compared to normotensive controls, indicating deficiency of these elements. For prevention of pre-eclampsia, it becomes necessary to know pathogenesis and factors that modify the course of the disease and its complications. Calcium, magnesium, and zinc might play an important role in this regard. Since there are changes in levels of these micronutrients, the estimation of these elements during pregnancy might become a possible index for early diagnosis and treatment of pre-eclampsia. It will be rationalistic to propose calcium, magnesium, and zinc supplementation during pregnancy to prevent pre-eclampsia and its complications.

Yet, as this study is done in a limited number of cases, further studies with larger groups and with supplementation of trace metals may be required to establish the fact.

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