Original article

Serum Calcium to Magnesium Ratio in Preeclamptic Women: A Cross-Sectional Study

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Abstract

Preeclampsia is a syndrome that adversely affects maternal and fetal outcomes. Despite extensive research, PE's exact pathogenesis is still uncertain. Micronutrients like calcium (Ca) and Magnesium (Mg) hemostasis were linked to many adverse health issues, including PE Herein, we aimed to verify the role of Calcium, Magnesium, and Calcium to Magnesium Ratio among PE cases vs. healthy controls for a possible application in preventive approach. The study enrolled 81 pregnant women whose age and body index matched and divided into two groups; PE cases and healthy controls. Their demographic, urine, and serum Calcium, Magnesium was compared. Analysis showed serum Ca2+ level, mean serum Ca2+-Mg2+ratio in the patients was considerably lower than in controls; P=0.01 and P=0.04, respectively. Reduced Mg levels were recorded only in PE cases. Correlation confirmed a positive correlation with maternal age and is inversely linked with gestational age, Ca 2+, Mg2+, and Ca2+-Mg2+ ratio. The diastolic blood pressure was negatively correlated to the Ca2+-Mg2+ ratio. Defining micronutrients during pregnancy and how this may affect maternal health is a promising avenue for PE prevention. Micronutrient profiling might help characterize preeclampsia prevention options.

Keywords: *Preeclampsia, Micronutrients, Calcium, Magnesium, Calcium to Magnesium Ratio, Prevention.*

Introduction

Preeclampsia PE is a prevalent medical illness that affects around 10% of pregnant women globally and can result in adverse pregnancy outcomes such as higher maternal-perinatal morbidity and morbidity defined as new onset hypertension in a previously normotensive pregnant after twenty weeks of gestation [1].

The pathophysiology of preeclampsia is unknown. Many speculated that a placental invasion defect and oxidative stress early in pregnancy were to blame. Biological trace elements are essential for human health [2].

The abnormalities in their homeostasis and metabolism play a vital role in many negative health effects. Trace elements also act as antioxidants, protecting the cell from harm [3].

A previous study has connected micronutrient deficiencies (zinc, copper, calcium, Magnesium) to the development of PE. However, the findings of certain studies on serum, Magnesium, calcium, and preeclampsia differed substantially [4,5].

The significance of trace elements in preeclampsia is critical for health planners and treating clinicians. Calcium and magnesium supplements, for example, might be used to avoid preeclampsia [6].

Magnesium (Mg+2) is an important micronutrient. It serves as a co-factor for many enzymatic systems. In cardio-vasculature system health, Mg+2 has a key role in blood pressure regulation as it affects the contractility and blood vessels' tone. Thus, blood vessels need Mg+2 to relax; and its deficiency is linked to PE development [7].

Calcium (Ca+2) is another micronutrient that plays a major role in maintaining blood pressure; the blood vessels need Ca+2 to contract. For that, a delicate balance has to be set for Mg+2 and Ca+2 to achieve normal blood pressure. Therefore, Mg+2 acts as a calcium-channel blocker by inhibiting intracellular calcium levels raise, which causes vasodilation [8].

Pregnancy requires an extra- supply of calcium and magnesium because of the fetal demand. Understandably, pregnancy-related physiological changes diminish their concentrations. Women destined to develop PE appear to have levels of those nutrients [9].

Approaches for minimizing the risk of PE disorders have received much attention. Until recently, studies on blood Ca2+ and Mg2+ concentrations in PE women have been conflicting, and studies on the serum calcium-magnesium ratio have been sparse.This study aimed to investigate micronutrients' role in PE development for a possible preventive role in practice.

METHODS

Between June 2020 and June 2021, an observational -cross-sectional study was conducted in the University hospital, recruiting 83 consented pregnant who gave their approval to participate after an explanation of the study's aim and methods was given. All methods were performed under the Helsinki tent. Participant were sub-grouped into 28 PE cases; diagnosed according to the American Heart Association criteria for diagnosing PE [10].
None of the PE cases had started an antihypertensive treatment. Another 53 Healthy controls (participants who were not hypertensive and did not have proteinuria) were randomly taken from the outpatient's department. Both sub-groups were gestational age and body mass index matched.

Exclusion criteria

Twin pregnancy and congenitally malformed babies, pregnancy complicated with growth restriction. Diabetic cases, mothers' renal, hepatic, and thyroid disease, and blood coagulopathy [11]. Drug use such as steroids, antibiotics and smoking, were all an exclusion. Any cases with incomplete data were excluded too.

Study flow

The basic anthropometric criteria and relevant clinical history were obtained by an interviewer questionnaire. A formal general; obstetrical examination was conducted; we measured blood pressure with a mercury sphygmomanometer while the pregnant was sitting at rest both systolic and diastolic blood pressure (SBP, DBP) were recorded. A sample of urine was taken for protein analysis.
A 5 mL of venous blood was taken and dispersed into a dry centrifuge tube. Xylidyl blue and O-cresolphthalein-complexones were the color markers employed in the spectrophotometric manual technique to assess serum calcium and magnesium. In the event of a delay, sample was stored at -20°C until examination time.
Urinalysis was done with a dipstick, which was a semi-quantitative approach.

Statistics

The data normality was checked by the Kolmogorov–Smirnov test. Data were expressed as means and standard deviations and numbers and percentages for continuous and categorical data, respectively. For categorical variables, univariate analysis was used. Unpaired t- student test was used to compare two different means. A binary logistic regression and Pearson correlation were used to assess the association between variables vs preeclampsia risk. IBM SPSS version 25 was used. A value of $P<0.05$ was considered significant in all.

RESULTS

This observational study enrolled 81 pregnant into two groups; PE cases (28/81) and Healthy pregnant (53/81). Regarding the demographic criteria, no significant differences were reported regarding maternal age, gestational age, and body mass index as $P>0.05$. The systolic and diastolic blood pressure were significantly higher in PE cases $P<0.05$, described in Table 1. The mean serum Ca^{2+} level of pregnant women suffering from PE was substantially lower than those recorded by normally pregnant women, 7.7 + 1.2 mg/dL vs. 9.1 + 0.7 mg/dL, P=0.01. Furthermore, the mean serum Ca^{2+}-Mg^{2+}ratio in the patients was considerably lower than in controls (3.3 ± 0.6) vs. (3.8 ± 0.40), P=0.04. Among PE cases, hypocalcemia was reported in 74.1% (20) vs. 14.8% (8) of controls. On the other hand, reduced Magnesium was recorded only in PE cases; reported in 3 (3.7 percent) of them. A statistically significant (P=0.01) is illustrated in Table 2 and Figure 1.

Table 1. basic demographic criteria of the study population

Variable	PE (n=28)	Controls (n=53)	P-value
Maternal Age (years)	28.4±6.82	26.3±4.85	0.49
Gestational age (weeks)	35.64±5.82	36.11±4.27	0.29
Body mass index (Kg/m^2)	29.13±3.07	28.38±3.8	0.31

Systolic BP (mm/Hg)	161.47±12.27	117.31±7.70	0.02*
Diastolic BP (mm/Hg)	105.4±6.63	81.33±7.49	0.03*

Table 2. Levels of Ca +2 and Mg+2 among study groups.

Variable		Preeclampsia n=28	Control n=53	Total (Prevalence)	P-value
Ca $^{+2}$ (mg/dL)	<8.6	20 (74.1)	8 (14.8)	28 (34.6)	0.01
	>8.6	7 (25.9)	46 (85.2)	53 (65.4)	
Mg^{+2} (mg/dL)	<1.46	3 (11.1)	0	3 (3.7)	0.01
	>1.46	24 (88.9)	54 (100.0)	78 (96.3)	
Ca2+ -Mg^{2+} ratio b	<2	0	0	0	0.04
	>2	54 (100)	27 (100)	81 (100)	

Ca2+ = calcium; Mg2+ = magnesium. Data are expressed as a number (percentages). b =non-significant differences since the Ca^{2+}-Mg^{2+} ratio category is constant.

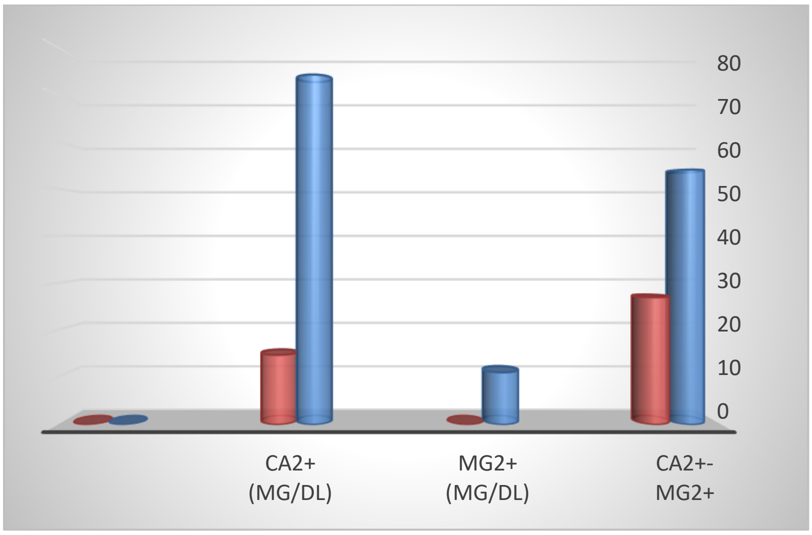

Figure 1: Prevalence of hypocalcemia and hypomagnesemia among study groups

Table 3: Comparison between PE (horizontal column) and control (vertical row) in different variables using Pearson correlation coefficient.

Factor	Age	GA	SBP	DBP	Ca $^{2+}$	Mg^{+2}	Ca^{2+}-Mg^{2+} ratio
Age	1	-0.025	0.47**	0.23	-0.21	-0.28	0.33
GA	–0.082	1	-0.145	0.17	0.16	-0.085	0.26
SBP	0.057	0.26	1	0.39 *	-0.39 **	-0.91	-0.17
DBP	0.09	-0.27	0.38 *	1	-0.49 *	-0.22	-0.27
Ca 2+	-0.03	-0.13	-0.175	0.049	1	0.49	0.17
Mg+2	0.18	-.028	-0.26	-0.19	0.21	1	-0.72 *
Ca2+-Mg2+ ratio	-0.20	0.099	-0.042	0.147	0.72*	-0.39	1

*a: Significant at 0.01, **: Significant at 0.05.*

GA: Gestational age, SBP: systolic blood pressure, DBP: diastolic blood pressure, Ca $^{2+}$ calcium, Mg^{+2} magnesium, Ca^{2+} -Mg^{2+} ratio: calcium/ magnesium ratio

Discussion

In normally pregnant women, serum Ca and Ca +2-Mg+2 ratio were significantly higher than in the women with preeclampsia. Our result was in line with earlier research in the field [12-14].

In PE cases reduced Ca levels result in higher renal renin release. The latter influences the maternal renin-angiotensin-aldosterone systems, consequently causing hypertension via vasoconstriction and fluid and/or Na retention[15].

Non renal renin-angiotensin systems are essential for uteroplacental and umbilical-placental circulation development. Because the action of maternal renin-angiotensin-aldosterone systems function is driven mainly by maternal demand. Calcium supplements among pregnant women showed a lower incidence of PE disorders and an increased neonatal birthweight[16].

Hypomagnesaemia was substantially higher in PE cases vs. controls. Reduced Mg+2 levels were associated with increased contractility and construction, leading to increased BP via reduced intracellular secretion of Nitric oxide, a vascular vasodilator[17]. Additionally, decreased Mg+2 levels allow free Ca+2 influx, thus exaggerating vessel constriction. The positive correlation result reinforced the former statement in our analysis. A delicate balance of Ca2+ and Mg2+ in PE must be tuned. Magnesium can be regarded as a Ca+2 channel blocker as it antagonizes the rise of intracellular Ca+2, thereby reducing vascular vasoconstriction[18].

The use of ratios is common in practice to increase the performance of two or more variables. Earlier research tested the Ca2+-Mg2+ ratio in evaluating seminal fluid analysis [19]. The neutrophil to lymphocyte ratio is an inflammatory biomarker that has been tested in PE, malignancy progression, and survival in acute emergencies [20].

Our analysis confirmed a lower Ca2+-Mg2+ ratio among PE cases vs. healthy controls. Moreover, the ratio was negatively and significantly correlated to SBP and DBP. Durlach et al. study discussed a lower Ca+-Mg+ ratio in PE cases during pregnancy [21]. Okoro et al. study confirmed a meaningfully lower Ca2+-Mg2+ ratio among PE cases compared to healthy controls. Idogun et al. study showed a trend of lower Ca2+-Mg2+ ratio; that did not show statistical value [22,23].

Preeclampsia-related complications could have long-term effects on the mother's and children's safety [24]. Despite substantial research, PE remains little understood; the identification of elemental micronutrients during pregnancy and how this may affect maternal health is promising. Elemental micronutrient profiling might help characterize preeclampsia prevention strategies. The WHO's advice for pregnant supplementation with calcium to reduce PE has to be reinforced[25].

We must acknowledge the current study's limitation; lack of sampling power, its cross-sectional design [26], and the effect of the COVID-19 pandemic have influenced many work aspects [27].

In conclusion, dietary sources of micronutrients, in addition to supplementary therapeutic preparation for preventing PE, is a promising option to be implemented in practice.

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