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### RESEARCH ARTICLE

#### STUDY OF SERUM CALCIUM AND CREATININE LEVELS IN PREECLAMPTIC WOMEN BELOW 35 YEARS IN A TERTIARY CARE CENTRE IN SOUTHERN ASSAM, INDIA.

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#### Abstract

Pre-eclampsia, a hypertensive multisystem disorder is one of the major causes of maternal morbidity and mortality. The exact aetiology is still unknown, though numerous hypotheses have been put forward. Studies have found that low serum calcium level may be associated with development of pre-eclampsia.

The aim of this study was to find the association between serum calcium level and pre-eclampsia by comparing the serum calcium levels in pre-eclamptic women with that of normal pregnant ladies. Our findings in this study indicate that pre-eclamptic women had a significantly lower serum calcium level than normal pregnant women ( $p < 0.01$ ) and creatinine level was found to be higher in preeclampsics. ( $p < 0.01$ ) This study concludes that low serum calcium level may be a causal factor for the development of pre-eclampsia. So, intake of mineral supplements like calcium may reduce the incidence of pre-eclampsia.

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#### Introduction:-

Preeclampsia syndrome, a hypertensive multi-system disorder either alone or superimposed on chronic hypertension forms the deadly triad, with hemorrhage and infection. It has often been labeled the "disease of theories" due to the numerous hypotheses that drive research into this complex disease (Solomon CG and Seely EW, 2004). This complication of pregnancy is one of the most common causes of maternal morbidity (Sukonpan K and Phupong V, 2005).

Preeclampsia is characterized by high blood pressure  $\geq 140/90$ , oedema and proteinuria. It typically occurs sometime in the second or third trimesters — after 14 weeks of pregnancy — with symptoms like swelling of the hands and face, and sudden weight gain. In severe cases, symptoms include nausea, vomiting, vision changes, headache, belly pain, haemolysis, elevated liver enzymes, thrombocytopenia, pulmonary oedema and foetal growth restriction [Chesley LC (1978)]. It is a pregnancy-specific syndrome characterized by variable degrees of placental dysfunction and a maternal response featuring systemic inflammation (Evans KN, *et al.* 2006). Studies suggest a failure of the trophoblastic invasion of the spiral arteries, leading to maladaptation of maternal spiral arterioles. This is associated

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with an increased vascular resistance of the uterine artery and a decreased perfusion of the placenta [Walker JJ(2000)].

The exact cause of preeclampsia is still unknown, despite considerable research.( Bringman J, *et al.*2006). The relationship between the aggravation of hypertension and the change in maternal serum level of various minerals during pregnancy have been shown in many clinical studies. (Kisters K, *et al.*2000). Modification of plasma calcium concentration leads to the alteration of blood pressure. The lowering of serum calcium and the increase of intracellular calcium can cause an elevation of blood pressure in pre-eclamptic mothers (Ray J, *et al.* 1999).

Also, various studies have reported elevated levels of serum creatinine in hypertensive disorders of pregnancy and also its effects on maternal and fetal outcomes. (Manjareeka M and Sitikantha N. ,2013).Serum creatinine levels are a part of work up for the hypertensive pregnant women .The elevated level of this parameter is due to decreased urinary clearance secondary to reduced GFR and increased reabsorption ( Jeyabalan A and Conrad KP,2007).

Research suggests intake of supplements, mainly calcium may help in the reduction of incidence of pre-eclampsia especially in a population of a developing country like India where the nutrition is poor.Hence, focus should be given more on prevention measures to manage preeclampsia. The present study aimed at measuring the serum calcium and creatinine levels in pre-eclamptic women and comparing the same with that of normal pregnant women.

### **Materials and Methods:-**

This hospital based case-control study was conducted on 200 pregnant women admitted in the indoor ward in the Department of Obstetrics and Gynaecology, SMCH, a tertiary care hospital, in southern Assam, India during July,2015-July,2016. They were divided into 2 groups comprising 100 normal pregnant women taken as controls and 100 pre-eclamptic women taken as study group. The pre-eclamptic patients were chosen in accordance with the American College of Obstetrics and Gynaecology guidelines. The normal pregnant women had normal blood pressure with no proteinuria. All subjects were primi below 35 years of age and >20 weeks of gestation. All maternal / foetal abnormal pregnancies (except pre-eclampsia), patients with essential hypertension, systemic or endocrine disorders and patients on calcium supplementation were excluded from the study. Written informed consent was taken from each subject and the study was approved by the Institutional Ethics Committee. Detailed family and medical history was taken from each patient. A thorough clinical examination was done on each subject and systolic and diastolic blood pressures were carefully recorded. Under aseptic precautions, 5 ml of venous blood was collected from each subject. The collected blood was allowed to clot spontaneously in a container, and then centrifuged at 3000 rpm for 10 minutes. Whenever possible, the analysis was done immediately. When there was a delay, the samples were stored at -20 degree till further analysis. After centrifugation, serum calcium and creatinine levels were estimated using standard procedures in AU-480 analyser in the laboratory of Biochemistry. The data obtained were tabulated and entered in MS Excel Worksheet. Data were expressed as mean  $\pm$  SD. Independent student t-test was applied for parametric variability considering  $p < 0.05$  to be statistically significant. Data analysis was done by Graph Pad InStat (Version 3.10).

### **Results:-**

The study was an observational hospital-based case control study of 100 preeclamptic (cases) and 100 normotensive pregnant (controls) of < 35 years of age conducted during July 2015 – July 2016. The study subjects were investigated for and results were analysed by using unpaired student's test which was two tailed.

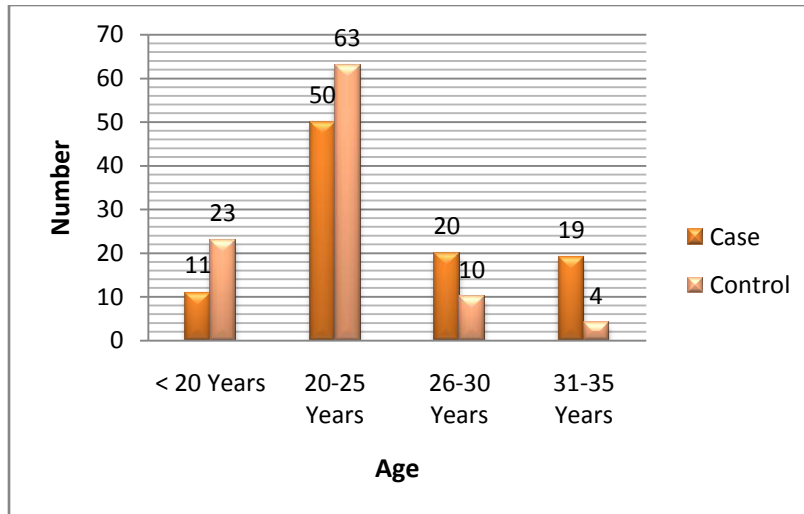


Figure 1:- Age distribution in case and control groups

The maximum number of subjects in each of the two groups was in the age group of 20-25 years. The maximum number of preeclampsics 63% belonged to the age interval of 20-25 years. Second largest group of preeclampsics (23%) were distributed in the age interval of <20 years. The other two age interval 26-30 years and 31-35 years contributed 10% and 4% respectively.

**Serum Creatinine:-**

Mean serum creatinine of cases and controls along with SD, SEM and p value given in following tables and figures.

Table 1:- Comparison of serum Creatinine in cases and controls.

	Mean	SD	SEM	95% CI for Mean	p-value
Cases	1.27	0.53	0.05	[1.16, 1.37]	<0.01
Controls	0.77	0.18	0.02	[0.73, 0.80]	

In the present study the mean serum creatinine level in cases was 1.27± 0.53 and in controls 0.77± 0.17. In the Unpaired t test between case and control groups, the two-tailed P value < 0.01 which is considered significant.

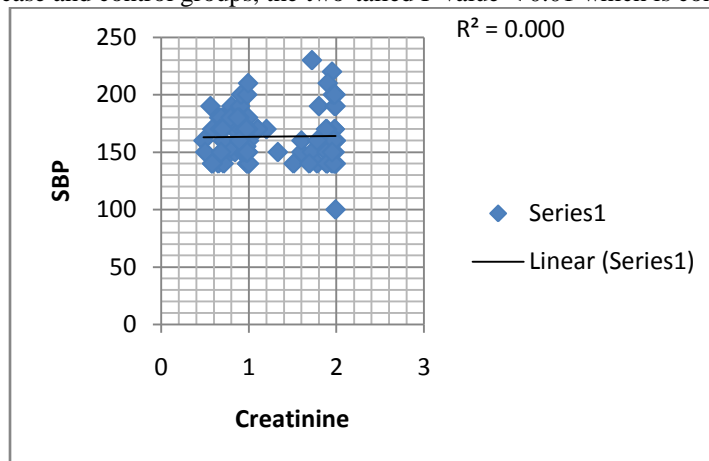
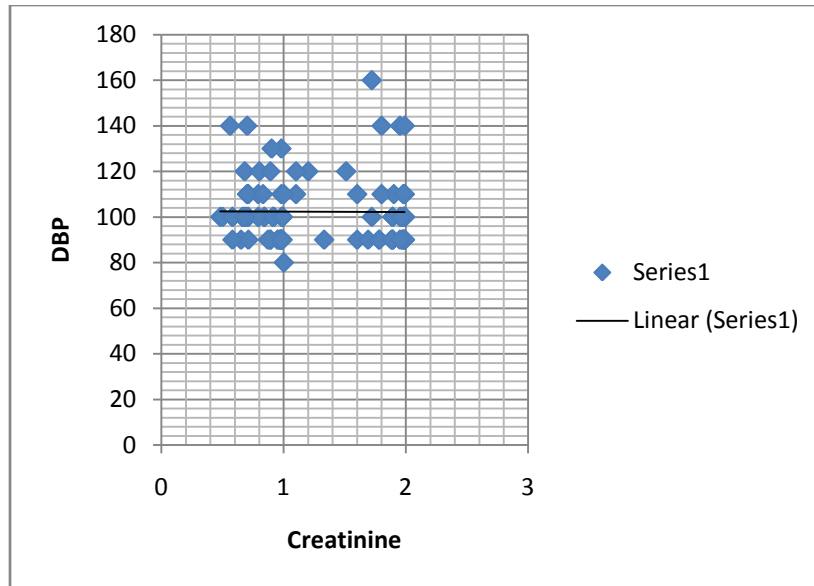


Figure 2:- Graph showing correlation between S.B.P. (Systolic blood pressure) and creatinine levels

R=0.02

Pearson’s correlation coefficient between systolic B.P. and creatinine is 0.02.R<sup>2</sup>=0.000

P value=.847, which indicates positive correlation, but it is not significant since p value>0.05.



**Figure 3:-** Graph showing correlation between D.B.P. (Diastolic blood pressure) and creatinine levels  
 $R = -0.007$ ,  $R^2 = 0.000049$   
 Pearson’s correlation coefficient between D. B.P. and creatinine is  $-0.007$ .  
**P value= .944**, which indicates insignificant correlation, since  $p \text{ value} > 0.05$ .

**Serum Calcium:-**

Mean serum calcium level of cases and controls along with SD,SEM and p value given in following tables and figures.

**Table 2:-** Comparison of serum Calcium in cases and controls.

	Mean	SD	SEM	95% CI for Mean	p-value
Cases	7.98	0.47	0.05	[7.89, 8.08]	<0.01
Controls	8.78	0.81	0.08	[8.62, 8.94]	

We found mean blood level of serum calcium in preeclamptic cases was  $7.9 \pm 0.47$  and in controls was  $8.7 \pm 0.81$ . In the Unpaired t test between case and control groups, the two-tailed P value  $< 0.01$  which is significant.

**Discussion:-**

Pre-eclampsia is associated with increased morbidity and mortality in developing countries but the exact cause of pre-eclampsia is still unknown. Several inferences can be drawn on the basis of the available results of this and other previous studies.

Our study assessing the serum calcium levels in pregnant women with and without pre-eclampsia showed serum calcium level to be significantly reduced in women with pre-eclampsia compared to normal pregnancy. This correlates well with the other studies ( Malas NO and Sheridan ZM, 2001).

Studies investigating calcium supplementation of pregnant women at risk of developing pre-eclampsia have shown that this intervention reduces the incidence and severity of the disease. An inverse relationship between calcium intake and hypertensive disorders of pregnancy was first described in 1980 and led to the hypothesis that an increase in calcium intake during pregnancy might reduce the incidence of high blood pressure and pre-eclampsia among women with low calcium intake (Belizan JM and Villar J, 1980).

Low serum calcium may predispose women to pre-eclampsia for the following reasons: (1) by increasing parathyroid hormone release and thus increasing vascular smooth muscle intracellular calcium, which promotes vasodilatation; (2) by stimulating renin release, which increases angiotensin II levels; (3) by decreasing serum magnesium levels, inducing vasoconstriction in vascular smooth muscle; (4) by diminishing the effect of endothelial

nitric oxide synthase, a calcium-dependent enzyme with vasodilatory action; and, finally (5) by reducing circulating prostacyclin, a calcium-dependent enzyme and a potent vasodilator. (Hofmeyr GJ, *et al.* 2010).

Recent evidence indicates that calcium supplementation affects uteroplacental blood flow (it lowers the resistance index in uterine and umbilical arteries). Supplementation in the second half of pregnancy appears to reduce blood pressure directly, rather than preventing the endothelial damage associated with pre-eclampsia (Hofmeyr GJ, *et al.*, 2010).

Calcium supplementation may play a beneficial role in the prevention of PIH by maintaining plasma ionized calcium levels within the narrow physiological range. Studies have shown that maintaining this range is crucial for the ongoing synthesis of vasoactive substances such as prostacyclin and nitric oxide in the endothelium and consequently for a normal endothelial function and thus lowering the blood pressure.

In one study by Deepa Kanagal *et al.*, the serum calcium concentration was significantly lower in the pre-eclamptic group compared to normotensives ( $7.84 \pm 0.87$  mg/dl Vs  $8.97 \pm 0.69$  mg/dl,  $p < 0.001$ ) (Deepa Kanagal, *et al.* 2014). Akhtar S *et al.*, in a study from Bangladesh showed significantly lower levels of calcium in pre-eclamptic women (Akhtar S, *et al.* 2011).

Jain *et al.*, Sukonpan and Phupong found a decrease in both serum calcium and magnesium in pre-eclamptic pregnant women as compared to normal pregnant women in their study thus supporting the hypothesis that hypocalcemia and hypomagnesemia are possible aetiologies of pre-eclampsia (Sukonpan K and Phupong V, 2005). A study from Northern part of India by Chaurasia *et al.*, found significantly lower levels of serum calcium and magnesium in pre-eclamptic women compared to normal pregnant women (Chaurasia PP, *et al.* 2012).

In the present study the mean serum creatinine level in cases was  $1.26 \pm 0.53$  and in controls  $0.76 \pm 0.17$ . In the Unpaired t test between case and control groups, the two-tailed P value  $< 0.001$  which is considered significant. Serum creatinine is a marker of GFR and renal dysfunction. Thus, in our study, we observed elevated levels of serum creatinine in preeclampsia when compared with normal pregnant women. This is in accordance with previous studies (Padma Y, *et al.* 2013).

The kidney is the organ most likely to manifest endothelial injury related to preeclampsia. Although the plasma creatinine concentration is generally normal or only slightly elevated (1.0 to 1.5 mg/dL (88 to 133 mmol/L), this could represent a decrease by 30–40% of glomerular filtration rate (GFR) for the values experienced in pregnant normotensive controls. Renal failure is an unusual complication that most often occurs in patients who develop severe preeclampsia. Progressive renal insufficiency i.e. serum creatinine concentration  $> 1.1$  mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease along with preeclampsia is a feature of severe preeclampsia (K. P. Conrad, *et al.* 2009).

Manjareeka *et al.* 2013, also found serum creatinine, expressed in mg/ dL to be significantly elevated in preeclamptics ( $0.72 \pm 0.387$ ) when compared to normotensives ( $0.58 \pm 0.283$ ) (Manjareeka M and Nanda S., 2016).

One study by Salako BL, found there was no significant difference in the mean values of uric acid and creatinine in the two groups. This was contrary to the findings of other workers that serum uric acid and creatinine levels are usually raised in patients destined to develop pre-eclampsia (Salako BL, *et al.* 2003). However, the inclusion criteria used in some of these studies were slightly different from those of the present study. Hayashi *et al.* demonstrated that abnormally high blood creatinine levels are seldom observed and those of uric acid often are normal even though the clearance was reduced in patient with preeclampsia (Hayashi T. and Philadelphia P., 1956).

### Conclusions:-

Our study shows a significant reduction of serum calcium level in pre-eclamptics compared to normotensives. This supports the hypothesis that hypocalcaemia may have a role in the aetiology of pre-eclampsia. It also emphasizes the need for monitoring the serum calcium level during the antenatal period so that appropriate measures may be instituted to reduce the incidence of pre-eclampsia.

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