

## A comparative study of serum uric acid, serum lactate dehydrogenase and serum calcium in hypertensive disorders of pregnancy and normal pregnancy

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### Abstract

**Introduction:** Hypertensive disorders of pregnancy (HDP) represents a group of condition with high blood pressure (BP) during pregnancy, proteinuria and in some cases convulsions. It complicates 5-10% of all pregnancy. Hyperuricemia due to oxidative stress is associated with deleterious effects on endothelial function, oxidative metabolism, platelet adhesion and aggregation. Calcium plays a critical role in the function of the cardiac and vascular smooth muscle. Patients with hypertension in pregnancy have benefitted from dietary calcium supplements. Lactate Dehydrogenase (LDH), an intracellular enzyme, is elevated in cell leakiness, hemolysis and cell death.

**Aim and Objectives:** To study serum Uric acid, LDH and Calcium in HDP and to compare with control. To study its correlation with systolic and diastolic BP in cases.

**Materials and Methods:** A study conducted on 50 cases and 50 controls selected according to inclusion and exclusion criteria. 3ml of venous blood was drawn to estimate the serum uric acid, LDH and Calcium levels in each subject. Unpaired 't'-test was used to study changes in the serum levels of uric acid, LDH and calcium in two groups. Pearson's correlation coefficient was applied to correlate serum uric acid, LDH and calcium levels with systolic and diastolic BP in cases.

**Results:** There was statistically significant increase in the levels of serum uric Acid, LDH and statistically decreased levels of serum calcium in cases as compared to controls.

**Conclusion:** Serum uric acid, LDH and calcium could be considered as a supportive diagnostic tool in HDP.

**Keywords:** Preeclampsia, Gestational hypertension, Eclampsia, Serum uric acid, LDH, Calcium.

### Introduction

Changes in Pregnancy include metabolic, biochemical, physiological, haematological and immunological processes.<sup>1</sup> Hypertensive disorders in pregnancy (HDP) represent a group of conditions associated with high blood pressure (BP) during pregnancy, proteinuria and in some cases convulsions.

Hypertensive disorders complicating pregnancy are one of the common and significant causes of maternal morbidity and mortality especially in developing countries. Various studies have concluded prevalence in India to be around 5–8%.<sup>2-5</sup> They complicate 5-10% of pregnancies in India.<sup>6</sup>

Various theories to explain the pathogenesis have been put forward. The main etiopathogenesis is placental implantation with abnormal trophoblastic invasion of uterine vessels & endothelial cell activation and dysfunction.<sup>7</sup>

Uric acid (2, 6, 8 – trihydroxypurine) is the end product of purine metabolism. Serum uric acid levels are typically elevated in HDP. It is likely to result from reduced uric acid clearance from diminished glomerular filtration, increased tubular reabsorption and decreased secretion. Another possibility is increased placental urate production compensatory to increased oxidative stress. Recently increased oxidative stress and formation of reactive oxygen species (ROS) have been proposed as another contributing source of hyperuricemia noted in Pregnancy induced hypertension (PIH) apart from renal dysfunction.<sup>8</sup> Uric acid

has deleterious effects on endothelium, oxidative metabolism and platelets. Serum uric acid levels increase very early at 10<sup>th</sup> week of gestation in patients who later develop preeclampsia.<sup>9</sup>

Lactate Dehydrogenase (LDH), an intracellular enzyme, is responsible for interconversion of pyruvate and lactate in the cells. Literature review suggests that progressive endothelial dysfunction in maternal vascular system induced by toxins released from hypoxic placenta causes profound vasoconstriction affecting all organ system including liver.<sup>10</sup>

Calcium (Ca), one of the abundant elements in the human body, plays a critical role in the function of the cardiac and vascular smooth muscles. Calcium has relaxant effect on pregnant uterus.<sup>11</sup> The lowering of serum calcium and its increase in levels of intracellular calcium can cause an elevation of blood pressure in preeclamptic mothers.<sup>12</sup>

Understanding of the underlying factors that explain the pathogenesis as well as early identification of the patients at risk will help in the development of preventive care or early therapeutic interventions. This in turn will help to reduce the associated morbidity and mortality during pregnancy and also the long term severe problems that are produced or associated with HDP.

### Materials and Methods

This cross sectional study was carried out in department of biochemistry of a tertiary care hospital from November

2014 to April 2016. 50 randomly selected patients with clinically diagnosed hypertension disorders in pregnancy with gestational age > 20 weeks attending outpatient department or admitted in Obstetrics Department of the tertiary care hospital were enrolled in the study. Accordingly 50 age matched single gestation pregnant females after 20 weeks with normal blood pressure were included as controls in the study.

Informed consent was obtained from participants enrolled in the study and approval from institutional ethical committee was taken before commencement of the study.

### Inclusion Criteria

**Age group:** 18– 45yrs.

1. 50 single gestation pregnant females after 20 weeks of gestation with blood pressure  $\geq$  140/90mm Hg, willing to participate in study.
2. Accordingly age matched single gestation pregnant females after 20 weeks with normal blood pressure were included as controls in the study.

### Exclusion Criteria:

1. Multiple gestation
2. Patients in active labour
3. Hepatic or renal disorders
4. Known seizure disorder
5. Known case of essential/chronic hypertension
6. Diabetes mellitus, cardiovascular diseases, stroke
7. Known medical disorders of gout & parathyroid gland disorder
8. Hemolytic diseases
9. Patients with increased nucleic acid turnover diseases. (e.g., leukemia, myeloma, radiotherapy, chemotherapy, trauma)

10. Patients on hepatotoxic drug, organic acids (e.g. lactate, acetoacetate), salicylate (low doses), thiazide diuretics
11. Smoking and alcohol intake

**Procedure:** After thorough history taking and clinical examination the procedure was explained to the subjects and an informed consent was obtained Blood pressure and proteinuria in the cases and controls were noted. 3 ml of venous blood sample (fasting) was collected from antecubital vein under all aseptic precautions in a plain bulb. It was allowed to clot and then centrifuged for serum separation. Serum was used for the analysis of serum levels of uric acid, LDH and calcium by Uricase PAP end point method, UV kinetic by DGKC principle, O- Cresophthalein complex one method respectively. The tests were done on the same day on ERBA chem 5 Semi automated analyser.

**Statistical Methods:** Data was expressed in terms of mean  $\pm$  SD. Unpaired 't'-test was used to study the changes in the serum uric acid, serum LDH and serum calcium levels.

P value > 0.05 was taken as non-significant.

P value < 0.05 was taken as significant.

P value < 0.01 was taken as highly significant.

P value < 0.001 was taken as highly significant.

Pearson's correlation coefficient was applied to correlate the values of serum uric acid, serum LDH and serum calcium with systolic and diastolic blood pressure.

### Results

The age distribution of cases and controls is depicted in Table 1.

**Table 1: Age distribution of cases and controls**

	Age Group (years)	Cases (series 1 in Fig. 1)		Controls (series 2 in Fig.1)	
		n	%	n	%
1	18 - 20	7	14	6	12
2	21 - 25	19	38	27	54
3	26 - 30	15	30	13	26
4	>30	9	18	4	8
	Total	50	100	50	100

The mean age (in years) of 50 cases was  $25.74 \pm 4.70$  and that of 50 controls was  $24.96 \pm 4.42$  ( $P > 0.05$ ) and was statistically non-significant.

The mean systolic blood pressure in cases and control group was  $152.48 \pm 9.24$  and  $113 \pm 5.78$  mm Hg respectively whereas the diastolic blood pressure was  $101.4 \pm 7.22$  and  $76.88 \pm 5.13$  mm Hg.

**Table 2: Comparison of serum uric acid, serum LDH and serum calcium levels between cases and controls.**

Group	Serum Uric Acid(mg/dl)	Serum LDH (IU/L)	Serum Calcium(mg/dl)
	Mean	Mean	Mean
Cases	$6.67 \pm 0.94$	$512.86 \pm 137.08$	$8.91 \pm 0.68$
Control	$4.2 \pm 1.11$	$226.8 \pm 70.26$	$9.84 \pm 0.59$
t	11.96	7.22	13.13
P	< 0.001	< 0.001	< 0.001

The mean serum uric acid levels in cases and in controls were  $6.67 \pm 0.94$  and  $4.2 \pm 1.11$  respectively and were very highly significant. ( $p < 0.001$ ) (Table 2, Fig. 1)

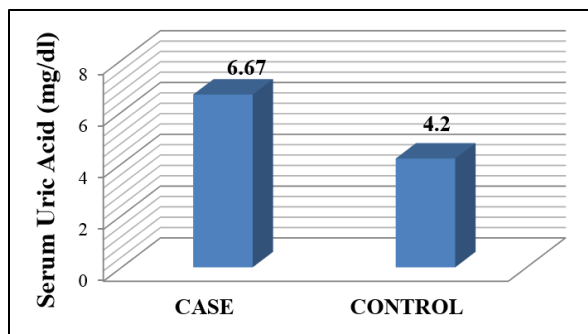


Fig. 1: Serum uric acid levels in cases and controls

The mean LDH levels in cases were  $512.86 \pm 137.08$  and in controls were  $226.8 \pm 70.26$ ; which was very highly significant ( $p < 0.001$ ). (Table 2, Fig. 2)

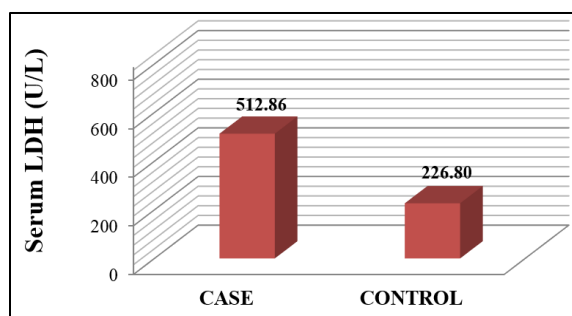


Fig. 2: Serum LDH levels in cases and controls

Table 3: Correlation of serum uric acid, LDH and calcium with the blood pressure in cases

Correlation	Values	Systolic Blood pressure	Diastolic Blood Pressure
Uric Acid	r	0.664	0.5487
	p	<0.001	<0.001
LDH	r	0.624	0.4852
	p	< 0.001	< 0.001
Calcium	r	-0.3963	-0.5123
	p	0.005	< 0.001

We found moderate positive correlation between serum uric acid and systolic blood pressure. ( $r = + 0.664$ ) which was highly significant ( $p < 0.001$ ). (Table 3)

There was a moderate positive correlation between serum LDH and systolic blood pressure ( $r = + 0.624$ ) which was highly significant ( $p < 0.001$ ). (Table 3)

Also, weak negative correlation between serum calcium and systolic blood pressure ( $r = - 0.3963$ ) was seen which was highly significant ( $p = 0.005$ ). (Table 3)

Moderate positive correlation was seen between serum uric acid and diastolic blood pressure. ( $r = + 0.5487$ ) which was highly significant ( $p < 0.001$ ). (Table 3)

There was a weak positive correlation between serum LDH and diastolic blood pressure ( $r = + 0.4852$ ) which was highly significant ( $p < 0.001$ ). (Table 3)

There was negative correlation between serum calcium and diastolic blood pressure ( $r = - 0.5123$ ) which was highly significant ( $p < 0.001$ ). (Table 3)

The mean serum calcium levels (mg/dl) in cases and controls were  $8.91 \pm 0.68$  and  $9.84 \pm 0.59$  respectively and were very highly significant. ( $p < 0.001$ ) (Table 2, Fig. 3)

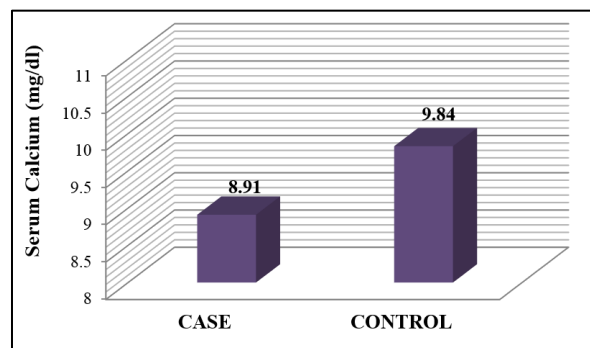


Fig. 3: Serum calcium levels in cases and controls

## Discussion

Hypertensive disorders of pregnancy are known since ancient times.<sup>13</sup> Hypertension is one of the common complications associated with pregnancy and contributes significantly to the cause of maternal and perinatal morbidity and mortality. Various traditional and newer biomarkers were suggested for diagnosis and prognosis of Hypertensive disorders of pregnancy. So, in view of greater emphasis being placed on maternal and child health in present era, the present study was undertaken. In this present study, we assessed the clinical utility of inexpensive biochemical markers like serum uric acid, serum LDH and serum calcium in HDP.

In this study, the mean  $\pm$  SD gestational ages of cases and Control were  $30.3 \pm 3.18$  week and  $29.7 \pm 3.36$  week and also majority of the patients (65%) were primigravida.

In our study, we found that the mean serum uric acid levels were significantly higher in cases when compared with controls. This finding is in accordance with the study

done by Punthumapol C et al,<sup>14</sup> Josephine,<sup>15</sup> Gandhi.<sup>16</sup> It is found that estimation of serum uric acid is as important as proteinuria in identifying the risk of renal involvement and fetal compromise.<sup>17</sup> High levels of uric acid are found to be a strong predictor of maternal disease progression and fetal outcome.<sup>18</sup> Many authors believed that uric acid is one of the most consistent and earliest detectable changing parameter that occurs in PIH and have been cited as a better predictor of fetal risk than blood pressure.<sup>9</sup> In contrast, Hickman et al concluded that the serum uric acid levels were unreliable indicator of developing hypertension in the individual woman.<sup>19</sup> Also, there was a positive correlation between serum uric acid with systolic ( $r = + 0.664$ ,  $P < 0.001$ ) and diastolic blood pressure ( $r = + 0.5487$ ,  $p < 0.001$ ). (Table 3). Similar findings were seen in studies done by Sonagra et al,<sup>20</sup> Saxena et al<sup>21</sup> and P Josephine et al<sup>15</sup> (Table 4). Mustaphi et al<sup>22</sup> and Varma<sup>23</sup> observed that when the levels of diastolic BP is increased, the levels of serum uric acid was also increased, concluding a positive correlation between diastolic BP and serum uric acid.

Correlation Coefficient  $r$  value with systolic BP in similar studies by Sonagra et al, Josephine et al, Saxena et al were 0.408, 0.287 and 0.214 respectively whereas  $r$  value with diastolic BP in same studies were 0.420, 0.235 and 0.367 respectively.

We found significantly elevated levels of serum LDH in cases as compared to controls. Similar results were seen in study by Gandhi M et al<sup>16</sup> they found a significant increase in serum LDH and serum uric acid levels in women with hypertension in comparison with normotensive women.

The finding was in accordance with study done by Umasatyasari Y et al<sup>24</sup> and Bera S et al.<sup>25</sup> Quablan H et al<sup>26</sup> concluded serum LDH can be used as a marker for prediction of adverse outcome of pregnancy in severe preeclampsia. A group of researchers have noted significant usefulness of amniotic fluid LDH levels at mid-trimester for prediction of IUGR.<sup>27</sup>

In our study, there was positive correlation between Serum LDH with systolic ( $r = 0.624$ ,  $p$  value of  $r < 0.001$ ) and diastolic BP ( $r = 0.4852$ ,  $p$  value of  $r < 0.001$ ) and was significant. (Table 4) Sonagra et al 2012<sup>24</sup> found  $r$  value of LDH with Systolic & Diastolic blood pressure as 0.504 and 0.546 respectively.

In this study, the mean serum calcium of the cases was  $8.91 \pm 0.68$  mg/dl, while the mean serum calcium of the control group was  $9.84 \pm 0.59$  mg/dl. There were statistically significant reduced levels of calcium in cases compared to controls. Similar findings were reported in other studies conducted in India and abroad.<sup>28,29</sup>

Thus, the results of previous epidemiological studies suggest that an inverse relation exist between calcium and incidence of hypertension in pregnancy.

The effect of serum calcium on changes in blood pressure could be explained by the level of intracellular concentration of calcium. Calcium takes part in muscle contraction and regulation of cellular water balance.<sup>14</sup> Low serum calcium stimulates parathyroid hormone and renin release which then increases the intracellular concentration

of calcium in the vascular smooth muscle. This causes vasoconstriction, increase of vascular resistance and rise in blood pressure leading to hypertensive pregnancy.<sup>29,30</sup> So the lowering of serum calcium and its increase in levels of intracellular calcium can cause an elevation of blood pressure in preeclamptic mothers.<sup>31</sup>

A meta-analysis from the epidemiology branch of the NHLBI found BP reduction with calcium supplementation from range 2 to 10 mmHg; which was primarily a systolic BP effect. Based on the NHLBI analysis, dose dependent the BP lowering effect was identified. Also BP lowering effect with increasing calcium intake was equally as great or even greater in normotensive subjects as in the hypertensive subjects.<sup>32</sup> The conclusion from the NHLBI analysis is consistent with the graphic portrayal of Grobbee's meta-analysis<sup>33</sup> and the conclusions of Mikami et al.<sup>34</sup>

In this study, there was negative correlation between serum calcium with systolic ( $r = - 0.3963$ ,  $p$  value of  $r = 0.005$ ) and Diastolic BP. ( $r = - 0.5123$ ,  $p$  value of  $r < 0.001$ ) and was significant.

We found Correlation Coefficient ( $r$ ) value of calcium with systolic & diastolic blood pressure as -0.3963 and -0.5123 respectively whereas study by Biswas S et al 2016<sup>35</sup> found  $r$  value of calcium with Systolic & Diastolic blood pressure as -0.1968 and -0.1843 respectively.

The difference with our result may be attributed to the different genetic pool of the population in which the studies had been done as compared to our population and also to the different dietary habits of the population.

## Conclusion

We found that serum uric acid levels and LDH levels were significantly higher whereas serum calcium level was significantly lower in cases as compared to controls group. Estimation of serum uric acid, serum LDH, and serum calcium is advisable in pregnancy for early detection and prevention of morbidity and mortality in mother as well as in the fetus in relation to HDP.

## Limitations

1. Sample size was small.
2. We did not correlate the parameters with different gestational age groups.
3. We did not estimate for levels of parameter in different classifications of hypertensive disorders of pregnancy and its complications.
4. The prognosis and mortality of the subjects was not considered.

**Conflict of Interest:** None.

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