

Usefulness of serum gamma glutamyl transferase in assessing severity of preeclampsia

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Abstract

Introduction: Pre-eclampsia is a multisystem disorder, unique to pregnant women after twenty weeks of gestation. In India the incidence of pre-eclampsia is reported to be 8-10% of the pregnancy. It contributes significantly to maternal and perinatal mortality and morbidity. Among the biochemical markers, uric acid and LDH have been extensively studied in pregnancy induced hypertensive disorders. Very limited studies are available about the role of GGT in preeclampsia. This study intended to know the correlate the biochemical levels of GGT, LDH and Uric acid with the severity of pre-eclampsia.

Materials and Methods: 50 pregnant women clinically diagnosed as preeclampsia after 20 weeks of gestation between 18-35 yrs of age group. Preeclampsia is diagnosed based on the American College of Obstetrics and Gynecology (ACOG) criteria. Cases were classified into two groups mild preeclampsia (Group II) and severe preeclampsia (group III). 50 Age matched healthy normotensive pregnant women after 20 weeks of gestation enrolled in the study as controls and categorized as Group I.

Results: Serum AST, ALT, LDH and uric acid levels were increased in cases compared to controls. Serum LDH is significantly increased in severe pre-eclamptic cases compared to controls. There was no significant correlation observed between GGT with serum LDH and Uric acid. ROC curve indicates that Serum LDH is the better indicator of severity in preeclampsia when compared to serum GGT and uric acid.

Conclusion: Serum LDH and uric acid are the better indicators of severity in preeclampsia when compared to serum GGT

Key words: Endothelial dysfunction, GGT, LDH, Preeclampsia, Uric acid

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Introduction

Preeclampsia is defined as being a pregnancy specific syndrome of elevated blood pressure (>140/90 mmHg) and proteinuria of >100 mg/dl by urine analysis or >300mg in a 24-hour urine collection, after 20 weeks of gestation¹. In India the incidence of pre-eclampsia is reported to be 8-10% of the pregnancy. It contributes significantly to the cause of maternal and perinatal mortality and morbidity. Preeclampsia is associated with many maternal complications such as eclampsia, HELLP syndrome, pulmonary edema, abruption placenta, postpartum circulatory collapse, acute renal failure, hepatic rupture, cerebral hemorrhage and visual disturbances².

It is known that preeclampsia is associated with vascular dysfunction. Many biochemical markers for vascular dysfunction have been studied in the maternal blood. It is also shown that oxidative stress in preeclampsia may further increase vascular damage and exacerbate the disease process³.

Among the biochemical markers, uric acid and LDH have been extensively studied in pregnancy induced hypertensive disorders. Hyperurecemia in preeclampsia is attributed to decreased renal clearance, associated hypovolemia and also increased reabsorption from kidney tubules. Hyperurecemia in preeclampsia is associated with adverse maternal and fetal outcomes⁴. Lactate dehydrogenase (LDH) is an intracellular enzyme which converts lactic acid to pyruvic acid and its elevated levels indicates cellular death and leakage of enzyme from the cell⁵.

The enzyme gamma glutamyltransferase (GGT) is an ectoenzyme which is widely distributed throughout the body in many tissues, particularly the liver. At the cellular level, significant activity occurs in both endothelium and epithelium. GGT has long been used as a marker for alcohol abuse and recently its physiological role has been studied extensively. Some experimental studies suggest that GGT is involved in production of free radicals and even within its normal range may be an early indicator of oxidative stress⁶. Association of GGT as a marker of endothelial function has been established in Diabetes Mellitus, Chronic Renal Failure and remodeling indices in chronic ischemic heart failure following MI^{7,8}.

This study examines the usefulness of biochemical parameters such as GGT, LDH and Uric acid levels in assessing the severity of preeclampsia. As severe preeclampsia causes numerous multisystem complications, we hypothesize that elevated levels of

serum GGT, LDH and uric acid may reflect the severity of preeclampsia and occurrence of complications.

Objectives

1. To estimate GGT, LDH and uric acid in preeclampsia cases and healthy control subjects.
2. To correlate GGT, LDH and uric acid levels with severity of Preeclampsia

Material and Methods

This case control study was conducted in Department of Biochemistry and OBG, Sri Devaraj Urs Medical College, a constituent institute of Sri Devaraj Urs Academy of Higher Education and Research and associated to R.L.Jalappa Hospital and Research Centre, Kolar. 50 Pregnant women clinically diagnosed as preeclampsia after 20 weeks of gestation between 18-35 yrs of age group visiting the obstetrics OPD and ward of R.L.Jalappa Hospital and Research Centre, Kolar were included as cases.

Preeclampsia was diagnosed based on the American College of Obstetrics and Gynecology (ACOG) criteria: a blood pressure $\geq 140/90$ mm of mg and proteinuria ≥ 300 mg/ 24hrs was observed on at least two occasions more than 6 hrs apart after 20 weeks of pregnancy. Cases were again classified into two groups mild preeclampsia (Group II) and severe preeclampsia (group III). Severe preeclampsia was classified if diastolic blood pressure increased to at least 110 mm Hg, Proteinuria > 5000 mg/day and presence of symptoms like headache, epigastric pain, visual disturbances, oliguria, elevated LFT, elevated RFT and thrombocytopenia. 50 age matched healthy normotensive pregnant women after 20 weeks of gestation were enrolled in the study as controls. Controls were categorized as Group I

Exclusion criteria: Cases with any medical history of systemic hypertension and diabetes before the

pregnancy, gestational diabetes, renal diseases, thyroid disease or liver disease were excluded from the study. Detailed informed consent was taken from all the subjects before participating in the study. This study was approved by institutional ethics committee.

Sample collection and analysis: After obtaining informed consent, 2 ml of venous blood was drawn from cubital vein under aseptic precautions. Blood was transferred to plain tube and allowed to clot. After clotting, serum was separated and used for the analysis of following biochemical parameters.

Estimation of Serum Gamma Glutamyl Transferase by IFCC method using L- γ -glutamyl-p-nitroanilide +glycylglycine as substrate⁹. Estimation of Serum LDH by IFCC method based on the LDH mediated conversion of lactate to pyruvate and coupled with oxidation of NADH. Oxidation of NADH, which is monitored by reflectance spectrophotometry used in drychemistry analyser⁹. Estimation of Serum Uric acid by enzymatic method using uricase in microslide method in vitros 250 drychemistry analyser¹⁰.

All the parameters were analysed in Vitros 250 Johnson & Johnson dry chemistry analyser in central clinical biochemistry laboratory in R.L Jalappa Hospital and research center. During the assay internal & external quality check was done on regular basis.

Statistical analysis

Descriptive data was represented as mean and standard deviation. Comparison of biochemical parameters between the cases and controls was done using One way ANOVA. Association of biochemical parameters with severity of preeclampsia was done using pearson's correlation analysis. All the statistical analysis will be done by using EPI Info statistical analysis package.

Results

Table 1: Comparison of physical and clinical parameters among study groups

Parameters	Group I Controls (N=50) Mean \pm SD	Group II Mild Preeclampsia (N=27) Mean \pm SD	Group III Severe Preeclampsia (N=27) Mean \pm SD	P- value
Age (Yrs.)	24.50 \pm 3.17	23.78 \pm 3.67	24.67 \pm 4.07	0.63
Gravidity (weeks)	37.10 \pm 3.412	37.82 \pm 2.01	36.71 \pm 2.44	0.39
Parity	2.12 \pm 2.97	1.47 \pm 0.84	1.75 \pm 1.00	0.48
Maternal weight (Kg)	64.28 \pm 4.39	69.17 \pm 4.47	70.57 \pm 13.81	0.00**
Systolic BP (mm Hg)	119.44 \pm 6.90	136.00 \pm 7.16	164.43 \pm 18.14	0.00**
Diastolic BP (mm Hg)	80.00 \pm 7.55	7.16 \pm 5.57	115.57 \pm 4.40	0.00**

** Highly significant

Table 1 represents the comparison of physical and chemical characteristics among the study groups. There was no statistical difference among the groups with respect to age, gravidity and parity. Mean values of maternal weight, systolic and diastolic blood pressure were significantly ($p=0.00$) increased in group III when compared to group I and II.

Table 2: Comparison of Biochemical Parameters among study groups

Parameters	Group I Controls (N=50) Mean±SD	Group II Mild Preeclampsia (n=27) Mean±SD	Group III Severe Preeclampsia (n=23) Mean±SD	P value
RBS (mg/dl)	81.52±13.45	84.4±16.3	90.4±29.8	P=0.185
S. Creatinine (mg/dl)	0.56±0.087	0.63±0.30	0.67±0.14	P=0.03*
Blood Urea(mg/dl)	13.0±4.60	18.3±20.0	19.1±10.0	P=0.185
Total Bilirubin (mg/dl)	0.38±0.15	0.66±1.5	0.60±0.47	P=0.290
AST (IU/L)	23.14±5-05	29.5±17.8	48.0±36.5	P=0.00**
ALT(IU/L)	17.9±4.2	26.5±15.5	30.6±18.6	P=0.00**
ALP(IU/L)	170.0±50.5	202±73.7	210.6±84.7	P=0.02*
Total Protein (g/dl)	5.8±0.67	5.6±0.6	5.5±0.7	P=0.31
Albumin (g/dl)	2.9±0.37	2.7±0.4	2.6±0.5	P=0.01*
Serum GGT (IU/L)	13.8±6.84	26.9±56.2	20.7±24.14	P=0.22
LDH (IU/L)	437.9±70.1	628.0±181.9	978.6±515.2	P=0.00**
Uric acid (mg/dl)	5.05±0.66	5.8±0.89	6.3±1.1	P=0.00**

*Significant ** Highly significant

Table 2 represents comparison of biochemical parameters among the study groups. Mean values of RBS and blood urea were more in group III patients when compared to Group I and II, but this difference was not statistically significant. Mean values of serum creatinine was significantly increased in group III patients compared to group I and II. Total Bilirubin was not statistically significant among the groups. Mean values of liver enzymes such as AST, ALT and ALP were significantly increased in group III when compared to group I and II. Mean values of total protein was not statistically different among the study groups, whereas serum albumin was statistically decreased in group III patients compared to group II and I. Serum GGT values did not show any statistical difference among the study groups, whereas serum LDH and Uric acid were significantly increased in group III and II when compared to group I.

Table 3: Correlation of Serum GGT, LDH and Uric acid

		GGT	LDH	Uric Acid
GGT	R value	1	0.97	0.09
	P value		0.50	0.53

Table 3 represents the correlation of GGT with LDH and Uric acid levels among the study groups. GGT was positively correlated with LDH and Uric acid but this was not statistically significant.

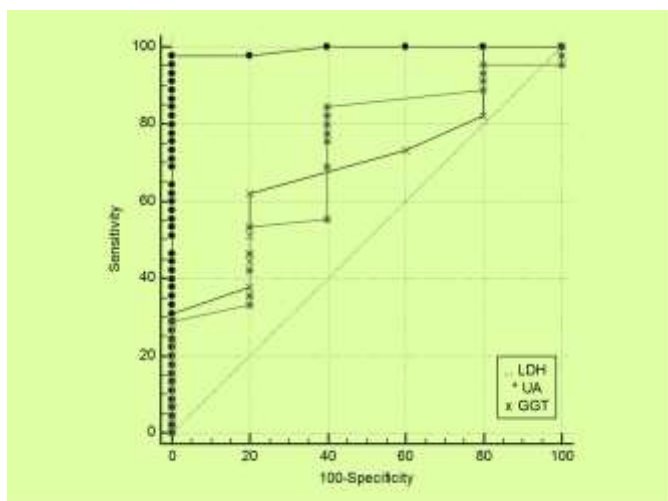


Fig: 1 ROC Curve for Sensitivity and Specificity of GGT, LDH and Uric acid for assessing severity of Preeclampsia

Fig. 1 represents sensitivity and specificity for LDH, Uric acid and GGT for assessing severity of preeclampsia. Serum LDH had highest area under curve of 0.993 followed by serum Uric acid 0.709 and GGT 0.696.

Discussion

Preeclampsia is a multisystem disorder. The exact mechanism is largely unclear. Many hypothesis suggest that the primary cause for preeclampsia is abnormal placentation and also impairment of maternal nitric oxide production leading to vasoconstriction and oxidative stress. These abnormalities eventually results in endothelial dysfunction. Many risk factors predispose to predispose to preeclampsia. Incidence is higher in women with maternal history of this disorder. Other risk factors include advanced maternal age (>35yrs), history of chronic hypertension, kidney disease, primigravida, previous history of preeclampsia, obesity, twin pregnancy, molar pregnancy and fetal congenital anomaly¹¹.

In the present study there was no statistical difference with respect to maternal age, gravidity and parity among the study groups. However maternal weight was significantly higher in mild and severe preeclamptic group compared to controls. Mechanism of occurrence of preeclampsia in obese women can be explained through insulin resistance which is associated with endothelial dysfunction. Insulin resistance also results in decreased nitric oxide production¹².

In the present study, serum creatinine, AST, ALT and ALP levels were significantly increased and serum albumin was decreased in mild and severe preeclamptic group. However there was no much difference in mean values of urea, total bilirubin and total protein among the study groups. A study by Ravi Babu et al., reported elevation urea, creatinine, AST and ALP in preeclamptic group¹³. Another study by S Paneri and others have also observed higher levels of serum urea, creatinine, AST, ALT and ALP in preeclamptic subjects. Hypervascularization and vasoconstriction in preeclampsia are the key factors in elevation of liver

enzymes. This also leads to reduced renal flow which leads to accumulation of urea and creatinine in maternal blood^{13,14}.

In the present study mean values of serum urea in mild and severe preeclamptic group is higher when compared to controls but this difference is not significant. This could be due to many factors which influence the serum urea levels such as diet, age etc.

Present study shows that serum GGT was not significantly different among the study groups. GGT is an ectoenzyme responsible for extracellular catabolism of glutathione, an intracellular antioxidant. The resulting amino acids are reutilized to synthesize intracellular glutathione. GGT is expressed in most of the tissues, but abundantly present in liver, renal tubules and intestine. GGT is conventionally been used as a marker for alcohol abuse, but there is scientific evidence that, GGT is associated with increased risk of death, major vascular and non-vascular outcomes, hypertension and diabetes. GGT is also known to be involved in generation of free radicals and causing oxidative stress^{15,16}.

Many studies have established association of GGT as a marker of endothelial dysfunction in preeclampsia^{17,18}. When GGT was correlated with LDH and uric acid, GGT levels were positively correlated with LDH and Uric acid, but this was not statistically significant. Present study did not show any association of GGT with the preeclampsia.

Larger portion of Serum GGT is mainly derived from liver. GGT from other tissues like kidney, pancreas and intestines also contribute to this. These isoforms of GGT derived from various tissues differ in physical and chemical properties¹⁹. Hence studying of tissue specific GGT isoforms would be more specific.

Serum LDH and uric acid levels were significantly elevated in mild and severe preeclampsia in comparison

with controls and was also supported by other studies by Amit D sonagra et al²⁰., Munde et al¹⁷., and Sakar et al¹⁸. LDH is elevated in preeclampsia due to cellular damage and leakage of enzyme from cell. Hyperurecemia is linked to reduced renal blood flow and impaired tubular reabsorption¹⁹. In the present study, it is observed in ROC curve that LDH and Uric acid are the better predictors of severity of preeclampsia compared to GGT. Thus biochemical markers such as LDH and Uric acid can be used as inexpensive laboratory tools to assess the severity of preeclampsia. However study of isoforms of GGT is suggested which is more specific and which can through a light on tissue specificity and organ damage.

Conclusion

We conclude that serum GGT is not a better biochemical marker compared to conventionally used markers like LDH and Uric acid. However study with the larger sample size and also studying isoforms of GGT may through a light on the specific organ damage in severe preeclampsia.

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