Scholars Journal of Applied Medical Sciences
Abbreviated Key Title: Sch J App Med Sci
ISSN 2347-954X (Print) | ISSN 2320-6691 (Online)
Journal homepage: https://saspublishers.com/journal/sjams/home

OPEN ACCESS

Biochemistry

Serum Cystatin C – A Better Marker of Preeclampsia

Dr. U.N. Priyadharshini[1], Dr. B. Shameem[2*]

[1,2]Assistant Professor, Department of Biochemistry, Govt. Mohan Kumaramangalam Medical College, Salem, India

***Corresponding author:** Dr. B. Shameem
| **Received:** 16.02.2019 | **Accepted:** 24.02.2019 | **Published:** 28.02.2019
DOI: 10.36347/sjams.2019.v07i02.052

Abstract **Original Research Article**

The purpose of this study was to determine whether the levels of cystatin c are significantly elevated in women diagnosed to have preeclampsia. We performed a case control study to compare the levels of cystatin c in women with preeclampsia (n=40) and normotensive antenatal women (n=40). Uric acid and creatinine levels were also compared. Serum Cystatin C estimation was done by nephelometry and the mean value was significantly higher in women with preeclampsia when compared to normal pregnancy (1.12±0.06mg/L and 0.69±0.03mg/L respectively). Uric acid levels were also significantly elevated in cases when compared to controls but there was no significant correlation between cystatin C and uric acid levels in cases (6.54±0.27mg/dl and 3.92±0.15mg/dl respectively). Creatinine levels were not elevated both in cases and controls (0.76±0.05mg/dl and 0.67±0.02 mg/dl respectively).
Keywords: Preeclampsia, Cystatin C, Uric acid, Creatinine.
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INTRODUCTION

Preeclampsia is best described as pregnancy-specific syndrome that affects virtually every organ systems and is recognized by new onset of hypertension and proteinuria that occur after 20 weeks gestation. It is estimated to complicate 2 to 8% of all pregnancies [1]. Pre-eclampsia has an immense adverse impact on maternal and perinatal health, especially in developing countries due to poor socio economic status which is one of the known risk factors [2]. Furthermore, pre-eclampsia and its adverse outcomes have been linked to higher risks of chronic non-communicable diseases (NCDs) in later life, thereby posing a daunting challenge within the context of double burden and limited resources in the developing world [3]. Preeclampsia is a disorder of widespread vascular endothelial malfunction and vasospasm associated with high maternal mortality and morbidity as well as risk of intra uterine death, preterm birth and perinatal death [4].

Preeclampsia is defined as Blood Pressure of 140/90mmHg or greater or an increase of 30 mmHg systolic blood pressure (SBP) or 15 mm Hg of diastolic blood pressure over the baseline value on at least two occasions. In addition to the blood pressure criteria, proteinuria of greater than or equal to 0.3 grams in a 24-hour urine specimen, a protein (mg/dL)/creatinine (mg/dL) ratio of 0.3 or higher, or a urine dipstick protein of 1+ (if a quantitative measurement is unavailable) is required to diagnose preeclampsia [4].Hypertension and proteinuria which remain as the important diagnostic criteria, develops only late in second or third trimester. Furthermore, varying diagnostic criteria are used in different regions of the world with disagreement regarding the degree of hypertension, presence or absence of proteinuria and class of disease severity. These inconsistence have led to changes in comparing and generalizing epidemiologic and other research findings [5].

It has been hypothesized that placental ischemia leads to placental production of soluble factors that cause maternal endothelial dysfunction. Renal glomerular endotheliosis is an essential component of the pathophysiological process in preeclampsia [6]. The kidneys play a significant role in turnover of low molecular weight substances such as Creatinine, Urate and Cystatin C [7]. Serum creatinine levels are elevated only after significant decrease in glomerular filteration, hence it is not reliable in early stages of renal impairment. Furthermore vasodilatation of renal vessels in pregnancy further complicates its use as marker of GFR in preeclampsia. Increased production of uric acid due to tissue breakdown in preeclampsia makes it a good predictive marker of eclampsia and fetal outcome [8].Its levels are influenced by diet and alcohol consumption. This disfavors the use of uric acid as a marker of renal impairment in preeclampsia. Urea levels are also not useful as it is affected by protein intake, liver metabolic capacity, renal perfusion and hydration [9].

Cystatin C is a non-glycosylated basic protein encoded on a house keeping gene. Its mRNA is found in every human tissue. It is freely filtered by the glomerulus then reabsorbed and catabolised by the renal tubules [10]. There are no extra renal routes of elimination. Plasma concentration of Cystatin C appears to be unaffected by muscle mass, diet or gender [11]. Studies in a number of patients have shown that serum cystatin c may be more sensitive and specific than serum creatinine value for signifying early changes in GFR [12]. So Cystatin C may play significant role as a sole biochemical marker for early diagnosis of preeclampsia.

MATERIALS AND METHODS

This is a Cross sectional Case – Control Study that was conducted after obtaining Ethical Clearance from the Institutional Ethical Committee. The study composed of 80 subjects attending the Obstetrics and Gynaecology Outpatient Department of Govt. Mohan Kumaramangalam Medical College Hospital, Salem. The study population consists of two groups – cases and controls. Cases consist of 40 antenatal women diagnosed to have preeclampsia beyond 20 weeks of gestation. Control group comprised of 40 age matched normotensive antenatal women coming to OPD. Controls were also matched for gestational age. Patients with previous H/O hypertension, diabetes mellitus, renal disorders and thyroid disorders were excluded from the study. After getting the written informed consent, baseline information and clinical history were obtained. 3ml of venous blood sample was collected and serum was separated. Serum Cystatin C level was estimated by immunoturbidimetry using the Turbodyne –cystatin c assay kit (Tulip Diagnostics) in a Nephelometer (Tulip Diagnostics). Intra and interassay % CV was less than 5% according to the procedure recommended by the reagent manufacturer. Serum Creatinine was estimated by Jaffe's method. Serum Uric acid was estimated by Uricase method. Liver Enzymes- Serum Aspartate aminotransferase and Alanine aminotransferase were estimated by modified IFCC method. These tests were performed in fully Automated Analyzer XL640.

RESULTS AND DISCUSSION

The study population consists of 80 subjects- 40 controls and 40 cases. Mean and standard deviation were estimated for each group (cases and controls). Data were expressed as Mean ± Standard deviation. The data were processed and analyzed using (SPSS) statistical software. Mean values were compared using student independent 't' test. The distribution of age among the control group and cases were equal. The details of descriptive parameters of the study population have been summarized in Table 1. There was no significant difference in mean gestational age among the cases and control. Mean Systolic blood pressure and diastolic blood pressure of preeclamptic women were higher than in control group.

Mean serum cystatin C level was higher in preeclampsia compared to control group (1.12±0.06mg/L versus 0.69±0.03mg/L) and was statistically significant. Serum uric acid was significantly higher in preeclampsia compared to control group (6.54±0.27mg/dl versus 3.92±0.15mg/dl). There was no significant difference in creatinine levels among cases and controls (0.76±0.05 versus 0.67±0.02) as depicted in Table 2. Pearson's correlation analysis was done to find out the relationship between cystatin c and creatinine among cases and was found to have no correlation as shown on Table3

Table-1: Clinical parmeters of study population

General characteristics	Mean ± standard deviation		P value
	Cases (n=40)	Controls (n=40)	
Age (years)	24.12±3.23	25.73±4.59	0.170
POG(weeks)	34.43±4.96	36.05±3.81	0.087
SBP(mmHg)	147.95±9.65	106.31±7.86	<0.001
DBP(mmHg)	117.34±8.12	75.64±7.04	<0.001

Table-2: Mean, Standard deviation, Test of significance of mean values between cases and controls

Biochemical parameters	Mean±Standard deviation		P value
	Cases	Controls	
Cystatin C (mg/L)	1.12±0.06	0.69±0.03	<0.001 Significant
Uric acid (mg/dl)	6.54±0.27	3.92±0.15	<0.001 Significant
Creatinine (mg/dl)	0.76±0.05	0.67±0.02	0.173 Not Significant

Table-3: Correlation of serum cystatin c and uric acid among cases

Variables	Pearson's correlation coefficient (r)	Significance (p)	Interpretation
Cystatin c vs Uric acid	0.36	0.123	No correlation

The pathogenesis of preeclampsia involves abnormal placental development, release of placental angiogenic factors, systemic inflammatory response and endothelial dysfunction. Kidney dysfunction may occur as a result of Glomerular endotheliosis which is characterized by swelling and vacuolization of endothelial cells with occlusion of the capillary lumen, leading to impairment of glomerular ultrafiltration [13]. Cystatin C1Qa is a cysteine protease inhibitor with a molecular weight of 13 kDa produced by all nucleated cells at a constant rate [14]. In our study cystatin c levels were significantly elevated in cases compared to controls but serum creatinine levels were not elevated both in cases and controls. Our data regarding both cystatin c and creatinine levels were consistent with the previous studies of Sumithra K *et al*. [15] and Anjana singh *et al*. [16]. Karl Kristensen *et al*. has demonstrated an increased expression of cystatin C in preeclampsia, with a good correlation to the clinical severity of the disease [17]

CONCLUSION

It is clear from this study that cystatin C has a significant role in the diagnosis of preeclampsia and in monitoring the severity of the disease. Further prospective studies can be done to find out how early cystatin c levels raises in preeclampsia. So it can be used as a biomarker for early diagnosis of preeclampsia.

Prophylactic measures like calcium supplementation, restriction of dietary salt intake, anti-hypertensives and low dose aspirin can be started early to reduce the maternal and perinatal morbidity [18].

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