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Predictive significance of serum Cystatin-C and serum lipids in preeclampsia

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Abstract

Introduction: Preeclampsia is a devastating pregnancy-associated disorder characterized by the onset of hypertension, proteinuria, and edema with limited plausible pathophysiology known. Cystatin-C, a novel marker for the detection of renal impairment, is increased in preeclampsia at an early stage. Moreover there is evidence of increased oxidative stress due to endothelial dysfunction in pre-eclampsia and increase in the oxidative stress is associated with abnormal lipid profile.

Objective: This study was aimed to evaluate the diagnostic efficiency of cystatin-C as an early marker of renal function and correlate with lipid profile in preeclampsia.

Materials and methods: The study was conducted on 80 pregnant women in third trimester who attended HMCH (O&G Department), Rourkela. They were divided in two groups A & B. Group A consisted of 40 normal pregnant women and Group B consisted of 40 pregnant women with preeclampsia.

Lipid profile was done by auto analyzer using recommended kit and cystatin-C by immunoturbidrimetric method.

Results: Serum total cholesterol, LDL, HDL showed no significant change in the two groups ($p>0.05$). However serum triglycerides levels were found significantly higher in preeclampsia patients when compared to normotensive pregnant subjects. Similarly serum cystatin-C was significantly higher in group B ($p<0.01$) and showed good correlation with lipid profile.

Keywords: Preeclampsia, lipid profile

Introduction

Pre-eclampsia, with a frequency of 3-7%, is a pregnancy related disorder constituting one of the leading causes of fetal and maternal morbidity and mortality world-wide [1, 2]. It is more frequent in nulliparous young women and in older multiparous women [3]. Pre-eclampsia is characterized by the new onset of hypertension and proteinuria occurring from 20 weeks of gestation onward [4]. Despite being one of the leading causes of the maternal morbidity and mortality, the etiology and pathogenesis of pre-eclampsia remain to be elucidated. Until date, endothelial dysfunction in the placental vasculature is considered as a widely accepted theory for the etiology and the pathogenesis of the disease [5]. Several other factors including genetic, immune, vascular and oxidative stress are also implicated in the pathogenesis of pre-eclampsia, which lead to the studies for identification of potential screening markers of the disease [6]. Studies in the field of cardiovascular research have shown that serum lipids have a direct effect on endothelial function and in this way abnormal serum lipid profiles are also associated with endothelial dysfunction. [7]. Recent published work have suggested that a maternal pre-disposition to pre-eclampsia may be explained by altered lipid profile, but the reported findings are inconsistent. [8, 9, 10]. Therefore, the present study was designed with the aim to investigate the alteration in serum lipid profile including total cholesterol, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides in pre-eclamptic and normal pregnant women.

The kidneys play an essential role, both in the adaptive physiology of normal pregnancy and in the pathophysiology of PE [11]. And some changes in renal function are found to be common to term pregnancy and PE [12]. But, the challenge to every clinician in the present context is to diagnose the renal impairment at an early stage to prevent this leading cause of fetal morbidity and mortality to progress into a severe stage (eclampsia) [13]. Creatinine is the most widely used biomarker of kidney function but is impervious in the early stages of renal impairment. Serum creatinine levels are elevated in patients with renal malfunction especially with the significant decrease in glomerular filtration. Vasodilation of the renal vessels in pregnancy causes 50–80% increase in plasma flow and change in glomerular filtration rate (GFR), which further

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Complicates the use of serum creatinine as a marker of GFR in pregnancy. All these explanations suggest that these traditional markers of renal function are unable to assess the renal impairment at an early stage and also to detect the reduced GFR in early stages of kidney dysfunction; hence search for new biomarker like Cystatin-C is suggested. In order to overcome this hindrance in estimating renal function in pregnant women, studies have demonstrated that serum Cys-C can reliably reflect the GFR in both healthy and hypertensive pregnant women [14].

Aims and objectives
This study was undertaken to see the diagnostic efficacy of serum cystatin-C as a marker of early renal impairment in PE and compare it with alteration in serum lipid profile including total cholesterol, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides in pre-eclamptic and normal pregnant women

Methods
The study was conducted in the Department of Obstetrics and Gynecology in collaboration of Department of Biochemistry, Hi-tech Medical College, Rourkela, Odisha, India after being approved by the Institutional Ethical Committee (IEC), HMCH. An informed consent was obtained from all the study participants. Renal function was investigated in two groups of pregnant women: one with preeclampsia, Group B (n = 40) and the other of healthy pregnant women, Group A (n = 40).
Relevant data were collected for blood pressure measurement and urine analysis at the beginning of the pregnancy to exclude preexisting proteinuria or renal disease. Maternal conditions potentially affecting GFR during the study (presentational hypertension, diabetes and other concomitant renal diseases) if present, were not included.

Blood samples were drawn from all the subjects following a fasting of 12 hours and analyzed for Serum Triglycerides (TG), Total cholesterol (TC) and HDL cholesterol (HDL-C) by enzymatic methods with the help of randox kits on Siemens auto analyzer. Serum LDL cholesterol (LDL-C) was calculated by Frederickson-Friedwald's formula according to which LDL cholesterol = Total cholesterol - (HDL cholesterol + TG/5). Serum Cystatin C was measured by immunotubidimetric method in ERBA Chem5 semi auto analyzer.

Data were statistically analyzed by Student's't' test and significance was expressed in term of 'p' value at 95% confidence level using Graph pad prism. Correlation coefficient (r) was also plotted online using Graph pad.

Results
Descriptive characteristics of the study participants are illustrated in Table 1. Overall, most of the study participants in both the study groups were multigravida and nullipara. Our study shows that the female developed PE in late gestational period (26.84 ± 5.20). The mean gestational age of pregnant women with PE was 28.7 ± 5.5. BMI was higher in preeclamptic patients than in control group (32.6 ± 6.1 versus 31.3 ± 5.3). Mean SBP and DBP (mm of Hg) were higher in preeclamptic patients than in control group (149.25 ± 9.7; 91.10 ± 4.75 and 116.35 ± 9.13; 75.35 ± 5.40, resp.)

Table 1: Age, BMI, systolic and diastolic blood pressures of pre-eclamptic and normal pregnant groups

| Physical variables	Group 1 (n=40)	Group 2 (n=40)
Age in years	28.4±5.3	28.7±5.5
Body Mass Index in kg/m^2	31.3±6.4	32.6±6.1
Systolic BP in mmHg	116.45±9.13	149.25±9.97
Diastolic BP in mmHg	75.35±5.40	91.10±4.75
Gestational age at blood sampling in weeks	25.1±5.3	25.4±5.6

All the lipid parameters were increased in preeclamptic group compared with the normal pregnancy group but all except triglycerides were statistically insignificant (Table 2).

Serum cystatin c level showed statistically significant increase in preeclamptic patients (Table 2).

Table 2: Comparison of serum total cholesterol, HDL, LDL, triglyceride and cystatin-C between the pre-eclampsia and normal pregnant groups.

Parameters	Group 1	Group 2	t statistics	p value
Total cholesterol (mg/dl)	162.05±14.75	166.58±13.87	1.42	0.16
Triglyceride (mg/dl)	130.45±11.02	165.78±19.13	10.13	<0.0001*
LDL (mg/dl)	83.9±17.43	85.25±12.09	0.4	0.69
HDL (mg/dl)	50.78±5.06	48.2±3.35	-2.68	0.09
Cystatin-C (mg/L)	1.19±0.14	1.39±0.06	8.31	<0.0001*

*Significant difference at $p<0.01$ at 95% confidence. HDL-High density lipoprotein, LDL-Low density lipoprotein
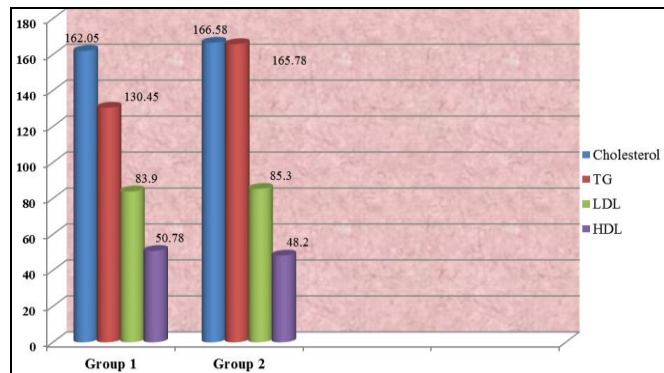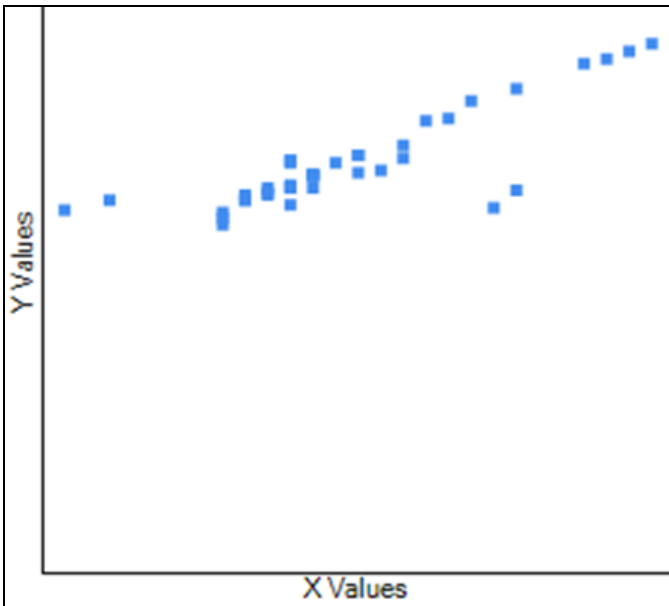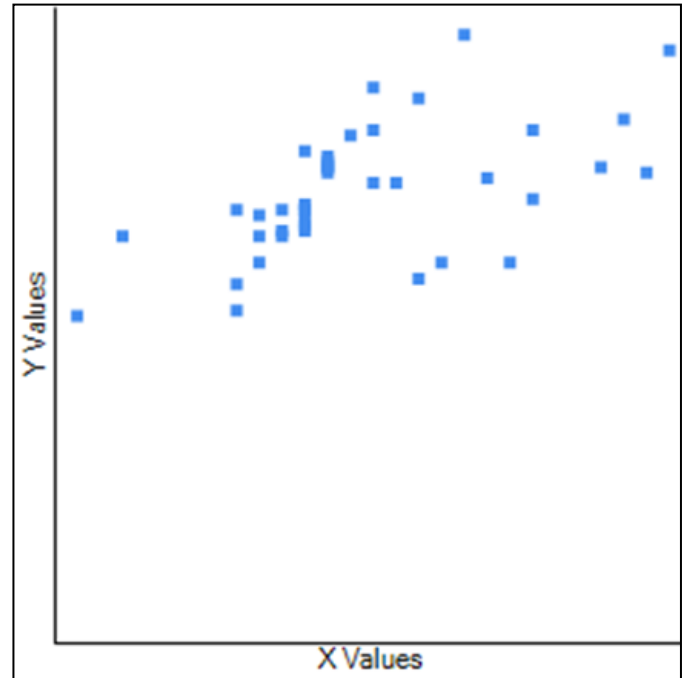

Fig 1: Lipid levels in Group 1 and 2
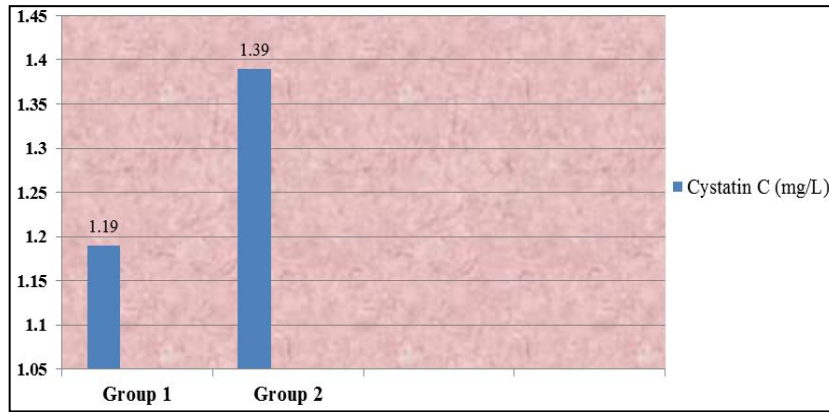
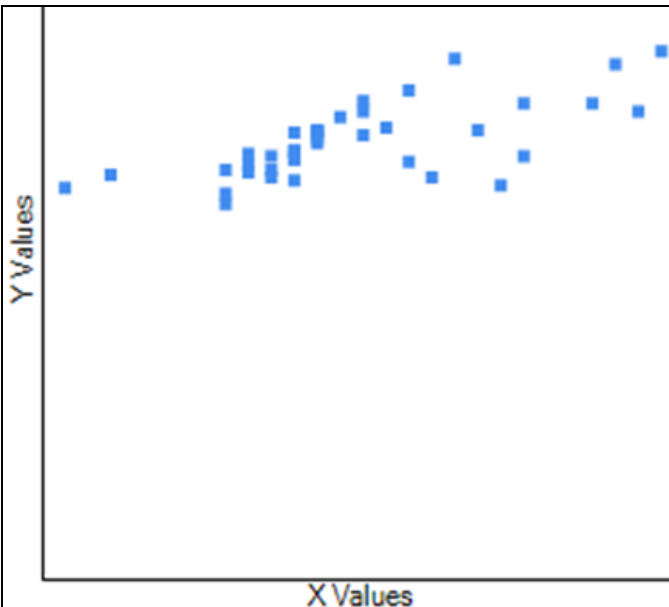**Fig 2:** Serum Cystatin C levels in Group 1 and 2

Figure 3-6 depicts the Pearson Correlation Coefficient Graphs plotted with serum cystatin C in 'x' axis and lipid parameters in 'y' axis. The correlation with TG (r=0.85) was strongest and with HDL (r= - 0.18) the weakest.
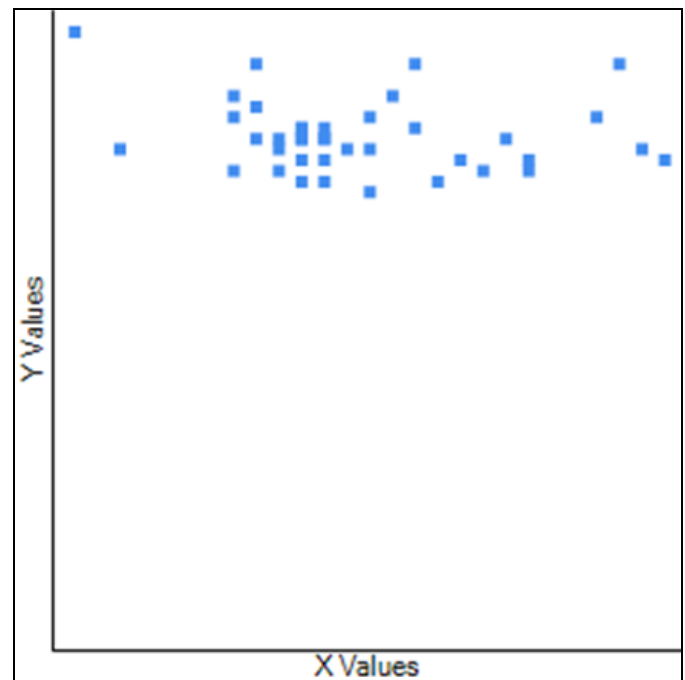

Fig 3: Correlation of cystatin C with TG (r = 0.85)

Fig 5: Correlation of cystatin C with LDL (r = 0.56)

Fig 4: Correlation of cystatin C with cholesterol (r = 0.68)

Fig 6: Correlation of cystatin C with HDL (r = -0.18)

Discussions

Renal impairment in PE has been implicated to various reasons, the most likely being hemodynamic changes [15]. And glomerular endotheliosis [16], as well as podocyte damage [17]. Our study showed that serum Cystatin-C was significantly higher in PE compared to control group. This finding was in accordance with [15, 18, 19]. Preeclamptic patients are at increased risk of renal impairment, though the dysfunction is usually under shadowed during the gestational period. The patients who developed PE are also at increased risk of developing PE in their subsequent pregnancies [20, 21]. The renal impairment if undiagnosed early can progress to renal failure and also lead to other vascular disorders later in life [22, 24]. Production of Cystatin-C might be increased during pregnancy due to an increased number of nucleated cells which is supported by a study showing serum Cystatin-C is increased during twin pregnancy [25]

Preeclampsia can be diagnosed easily by determining hypertension with proteinuria, but the diagnosis of the true condition associated with the increased risk can still be elusive, as pregnant women can present with hypertension and proteinuria due to other conditions as well, and a preeclamptic state can be present without raised blood pressure or albuminuria. Moreover, blood pressure levels and proteinuria are unstable markers, often varying within a wide range during the course of the disease. The estimation of serum Cystatin-C could be helpful in the diagnosis of PE, reflecting a different feature of the disease as a stable indicator of an altered filtration process and may also prove valuable for the monitoring of GFR in renal disease in pregnancy and in PE

The results of our study have shown that there are no statistical differences in total cholesterol, HDL and LDL concentrations between pre-eclamptic women and normal pregnant women, therefore not related with the diseases. However, elevated serum triglycerides might be involved in the endothelial damage leading to pre-eclampsia. Moreover raised serum triglycerides can be used as screening marker in early stages of pregnancy for the development of pre-eclampsia later.

The most important finding of our study however is the fact that we have found a strong relationship between serum triglyceride and serum cystatin C both of which increased significantly in preeclamptic patients. There are no other studies in our opinion which have found a strong correlation between these two parameters.

Conclusion

Preeclampsia is still a leading cause of maternal morbidity and mortality in both developed and underdeveloped countries. Renal dysfunction plays an initial and central role in pathophysiology of PE. Hence, assessment of renal function plays a vital role in monitoring and prediction of severity in PE. Therefore an early marker of renal impairment is needed in the diagnosis and thereby preventing progression of PE to eclampsia. The relation between TG and cystatin C should be further evaluated to confirm our findings. Evaluation of TG and cystatin C together can hence be of immense help in early detection of preeclampsia.

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