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SERUM CYSTATIN C– CORRELATION WITH CARDIOVASCULAR COMPLICATIONS IN DIABETIC POPULATION

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ABSTRACT

Background: The estimation of Serum Cystatin C has become widely available in clinical practice. Though Cystatin C is an approved marker of renal dysfunction in diabetic population, its role is evolving as a marker of cardiovascular mortality as well as neuro-degenerative disorders like Alzheimer's disease.

Aim: The present study aims to establish the predictive role of Cystatin C in cardiovascular complications and hence its role in as a marker of cardiovascular mortality in a diabetic population.

Methods: 144 patients fulfilling inclusion and exclusion criteria were enrolled in the study over a period of 3 months. Details of socio-demographic data, clinical variables and biochemical parameters were collected using a semi-structured proforma specifically designed for this study. Relevant clinical tests were done and data thus collected was tabulated and analysed using SPSS. Conclusion: There is a significant correlation of elevated Serum Cystatin C and cardiovascular complications. It has a strong positive predictive value for cardiovascular mortality in diabetic population.

Keywords: cardiovascular complications, Diabetic population, Serum Cystatin C,

INTRODUCTION

Diabetes is an important health problem in both the developed and developing countries. It is a common, often asymptomatic but readily detectable condition. When left untreated it leads to accelerated atherosclerosis and target organ damage involving the heart, brain, eyes, kidneys and the peripheral blood vessels.[1]

The U.S. Preventive Services Task Force recommends screening for abnormal blood glucose and type 2 diabetes in adults of age group between 40 to 70 years. All who are overweight or obese and repeating testing every three years if results were considered normal. Individuals at higher risk should be considered for earlier and more frequent screening. The fasting plasma glucose test (FPG) or the hemoglobin A1C test can be used for screening.[2]

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The American Diabetes Association recommends that anyone with a body mass index higher than 25 (23 for Asian Americans), regardless of age, who has additional risk factors, should be screened for diabetes.[3]

As mentioned above, untreated diabetes can lead to numerous long term and lethal complications. Target organ damage can occur in form of cardiomegaly (left ventricular hypertrophy), Coronary heart disease, cerebrovascular accident, retinopathy, nephropathy and peripheral vascular disease. Hence, screening, early detection and prompt treatment is vital to ensure prevention of target organ damage.[4] Large screening programs and information regarding diabetes may be the most important factor in reduction of mortality over the past 2 decades.[5]

Even though the diagnosis of Diabetes itself is easy, there is a need for predictive markers to assess the risk of target organ damage and associated risk of cardiovascular mortality. Microalbuminuria, Lipid profile abnormalities, Apolipoprotein levels and C-Reactive protein levels have emerged as practical markers to predict target organ damage.[6] However, they have other confounding factors. Hence the need to identify novel markers to risk stratify the diagnosed cases of Diabetes cannot be over-emphasised.[7]

Cystatin C is a protein encoded by the CST3 gene, is mainly used as a biomarker of kidney function. Recently, it has been studied for its role in predicting new-onset or deteriorating cardiovascular disease. It also seems to play a role in brain disorders involving amyloid (a specific type of protein deposition), such as Alzheimer's disease. In humans, all nucleated cells produce cystatin C as a chain of 120 amino acids. It is found in virtually all tissues and body fluids. It is a potent inhibitor of lysosomal proteinases and probably one of the most important extracellular inhibitors of cysteine proteases.[8]

Although studies are somewhat divergent, most studies find that cystatin C levels are less dependent on age, gender, ethnicity, diet, and muscle mass compared to creatinine, and that cystatin C is equal or superior to the other available biomarkers in a range of different patient populations, especially diabetic patients.[9] Additionally, the age-related rise in serum cystatin C is a powerful predictor of adverse age-related health outcomes, including all-cause mortality, death from cardiovascular disease, multimorbidity, and declining physical and cognitive function.[10]

Hence, we propose to do a study to determine the prevalence of elevated Cystatin C levels in diabetic patients and to see if it correlates with the target organ damage such as cardiomegaly, ischemic heart disease and biochemical parameters like lipid profile.

MATERIALS AND METHODS

It is a Cross-sectional study. The study sample comprised 144 diabetic patients enrolled over a period of 3 months.

Selection criteria:

1. Diabetic patients irrespective of duration
2. No proteinuria on conventional dipsticks
3. Normal serum creatinine levels

Ethical consent:

Ethics committee approval was obtained before proceeding with this study. The study was carried out as per the tenets of the 1964 declaration of Helsinki. Participation was voluntary

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and no incentives were provided. Informed consent was taken from the patients before their inclusion in the study and they were assured of the confidentiality of their answers.

Details of socio-demographic data, clinical variables and biochemical parameters were collected using a semi-structured proforma specifically designed for this study. Relevant clinical tests to detect target organ damage viz. Electrocardiogram, echocardiogram, Serum Creatinine, Serum Cystatin C levels were done and data thus collected was tabulated and analysed using SPSS. The final data was analysed using Chi-Square test and Regression analysis methods. Value of 'p' was considered less than 0.05 by chi-square test and value of "R' more than 0.4 by regression analysis was considered significant.

RESULTS

The prevalence of elevated serum cystatin C is 51 out of the 144 patients studied with similar trends noted in both genders.

Table 2 reveals presence of elevated serum cystatin C levels in 31 patients of obesity.

There is increased incidence of elevated cystatin C levels among diabetic population suffering from cardiovascular complications. The distribution with different cardiac complications is summarised in Chart 1.

There is a strong correlation between Cholesterol levels and serum cystatin C levels as tabulated in Table 3.

The prevalence of elevated serum cystatin C levels in diabetic hypertensive population was 35.42%, higher than the international estimates but correlating well with other Indian studies. There was a statistically significant relation between obesity (BMI> 25) and the prevalence of elevated serum cystatin C levels.

Presence of elevated serum Cystatin C has a significant correlation with cardiovascular complications like Left ventricular hypertrophy and ischemic heart disease. There was a significant correlation between elevated serum cystatin C levels and dyslipidaemia.

DISCUSSION

Before we start the discussion, few aspects of this study need to be clarified. This study is a cross sectional study, hence the severity or control of diabetes over a period of time cannot be assessed. Most studies regarding serum cystatin C are done in western countries. In comparison the studies in India are very small in number as well as population size of the study.[11]

Serum Cystatin C and other biomarkers were measured in participants in the LIPID (Long-Term Intervention with Pravastatin in Ischemic Disease) study. Cystatin C independently predicted major cardiovascular events, development of chronic kidney disease, and cardiovascular and all-cause mortality as per the study. Hence, we made comparisons with results of these studies to our present study. The prevalence of elevated serum cystatin C levels in diabetic hypertensive population was 35.42%, higher than the international estimates but correlating well with other Indian studies. There was a statistically significant relation between obesity (BMI> 25) and the prevalence of elevated serum cystatin C levels.

Presence of elevated serum Cystatin C has a significant correlation with cardiovascular complications like Left ventricular hypertrophy and ischemic heart disease. There was a significant correlation between elevated serum cystatin C levels and dyslipidaemia.

In our study (as noted in Table 1), the prevalence of elevated serum cystatin C was 35.42% which correlated with the Indian study by Arivandaksham p et al[12] and multiethnic study done

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by Bui AL et al.[16] No other Indian study in similar form was identified. The prevalence was found higher than that in the LIPID[13] study. This highlights the probable delay in the diagnosis and institution of treatment for diabetes in the sub-continent.

The study also noted an increase in the prevalence of elevated cystatin C levels with increased duration of diabetes. Statistically significant relation between Obesity and elevated serum Cystatin C levels was noted in the study (table 2). This correlates with results mentioned by Kohler K et al[14] and Ying-Xiang Huo et al[15] in their population study. Obesity is associated with hyperinsulinemia which contributes of endothelial dysfunction and is the postulated hypothesis for the increase in incidence of Serum Cystatin C levels.

Correlation between cardiovascular complications and elevated serum cystatin C levels (table 3) was found significant. This correlates with the LIPID study.[13] The study found that patients with albuminuria had a larger left ventricular mass and a higher degree of LVH.[13]

Results of the study as tabulated in table 4 also suggest a positive correlation with parameters of the lipid profile. Pramodkumar et al [12] had noted that in diabetic population.

Conclusions:

Based on the findings of the present study, we can conclude that the Predictive value of Serum Cystatin C in predicting cardiovascular complications is 92.15%, while, the predictive value of a negative test is 85.48%. Estimation of Serum Cystatin C levels should be done routinely in diabetic population for early detection of CKD as well as CVS complications. This will allow risk stratification of diabetic population especially at the time of diagnosis. This can help in appropriate allocation of healthcare resources in evaluation of cardiovascular complications in a diabetic population.

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TABLES

Level	Total patients		Male		Female	
	N	%	N	%	N	%
Elevated Cystatin C	51	35.42	34	36.17	17	33.33
Normal Cystatin-C	93	64.52	60	63.83	33	35.48
Total	144	100	94	100	50	100

Table 1: Population and Gender distribution of elevated serum Cystatin C levels

Level	BMI			
	<25	25-30	>30	Total
Elevated Cystatin C	4	12	15	31
Normal Cystatin C	71	34	8	113

Table 2: Correlation between Cystatin C levels and BMI (Body Mass Index)

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Lipid Profile (Mean Values)	Elevated Cystatin C	Normal Cystatin C	'R' value	Regression analysis 'R' value > 0.4
a. Cholesterol	208.25	157.92	0.430	Significant
b. Triglycerides	155	113.58	0.269	Non-significant
c. HDL	40.21	42.98	0.216	Non-significant
d. LDL	118	84.81	0.435	Significant

Table 3: Correlation between Cystatin C levels and Lipid Profile

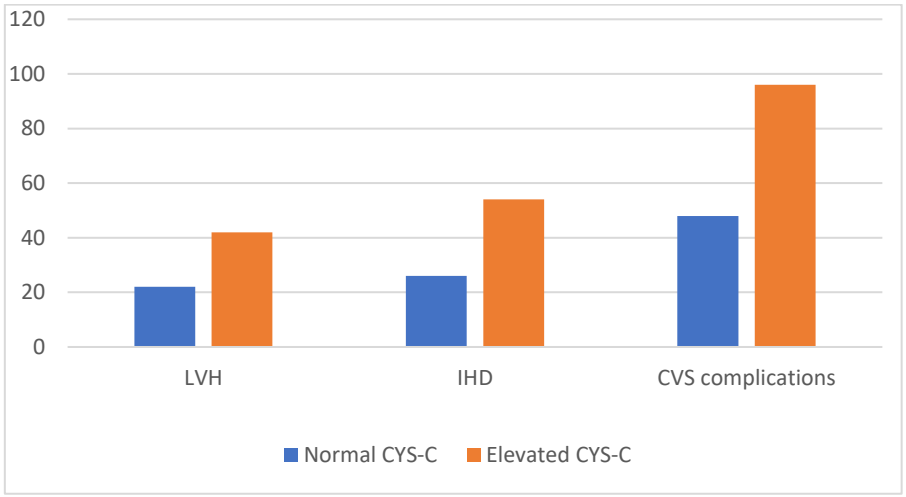

Chart 1: Correlation of elevated cystatin C with cardiovascular complications