

Study of Early Renal Dysfunction in Type 2 Diabetics with Special Reference to Serum Cystatin C Levels and Microalbuminuria

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Abstract: India is becoming Diabetic capital of the world with a parallel increase in long term complications associated with Diabetes. This study was done to evaluate Cystatin C as a marker for detecting early renal dysfunction in Diabetic Nephropathy. Serum Cystatin C and Urine Albumin levels were measured in 100 type 2 Diabetics alongwith other parameters like FBS, HbA1c, Serum Urea and Creatinine, blood pressure and lipid profile. e GFR was calculated using CKD-EPI equations. Mean Cystatin C concentrations showed stepwise statistically significant increases as eGFR reduces and also increases with increasing level of albuminuria ($p < 0.001$). Among normoalbuminuric patients ($n = 46$), 17.4 % patients were having increased Serum Cystatin C as compared to 4.3% patients having increased Serum Creatinine ($p < 0.001$). In ROC analysis, area under curve of Serum Cystatin C is 0.758 ($p < 0.001$) which signify that Serum Cystatin can be a fair predictor of Nephropathy. Glycemic control, blood pressure and dyslipidemia were directly related with albuminuria and eGFR. This study supports the use of Cystatin C for detecting early renal dysfunction as compared to conventional markers.

Keywords: Cystatin C, Diabetic Nephropathy, Albuminuria, Diabetes.

INTRODUCTION

The exponential rise in global prevalence of Diabetes and its associated long term complications have become a public health problem of considerable magnitude. Because of the huge premature morbidity and mortality associated with this disease, prevention of complications is a key issue in Diabetes management.

Diabetic Nephropathy is one of the leading causes of chronic renal failure in India contributing to over 30% of cases [1]. In the last 50 years, blood urea and serum creatinine estimation have become the most commonly used serum markers of renal function. Due to the unfavourable prognosis of advanced stages of Diabetic Nephropathy (DN), the ideal approach is to identify renal involvement as early as possible. Microalbuminuria is regarded as the gold standard for diagnosing the onset of Diabetic Nephropathy. However, about 10% of subjects with type 2 Diabetes Mellitus (DM) will have low GFR without micro- or macroalbuminuria[2].

Cystatin C is a 132 amino acid, 13-kDa cysteine protease inhibitor produced by all nucleated cells, whose function is thought to be modulation of the intracellular catabolism of proteins. It is formed at a constant rate and is freely filtered by the renal

glomeruli, fulfilling an important criterion for any endogenous marker of GFR [3].

In this study we aim to find the diagnostic accuracy of Serum Cystatin C as an early marker for detection of Diabetic Kidney Disease. We evaluated the association of Serum Cystatin C with Serum Creatinine, albuminuria and eGFR. Creatinine and eGFR Cystatin.

MATERIALS AND METHODS

The present study entitled "Study of Early Renal Dysfunction in type 2 Diabetics with special reference to Serum Cystatin C levels and Microalbuminuria" was carried out in 100 type 2 Diabetic patients admitted in Medical Wards, Department of Medicine of S.S. Medical College & associated SGMH, Rewa.

Information regarding name, age, gender, Albuminuria, Fasting Blood Sugar, HbA1c, Serum

Creatinine, Serum Urea, Serum Cystatin C, High density lipoprotein, Low density lipoprotein, Triglyceride, Total Cholesterol, Systolic and Diastolic blood pressures was noted using a pre designed proforma.

Inclusion Criteria

All type 2 Diabetics with duration of disease less than 10 years

Exclusion Criteria

- Pre existing renal disease
- Post renal transplant
- Patients on steroids or cyclosporine
- Chronic liver disease
- Congestive cardiac failure
- Patients with gross proteinuria
- Patients with thyroid disease

Sample size: 100 patients

Procedure Plan

Analysis of Proforma
 Estimated GFR (eGFR) will be calculated using CKD – EPI equation.

RESULTS

The study cohort was divided into groups based on urine albumin excretion as normoalbuminuria (n=46), microalbuminuria (n=33) and macroalbuminuria (n=21). The baseline characteristics of the patients are shown in Table 1.

- Most common age group among Normo, Micro and Macro group was 51-60 years .There was a significant (p=0.043) age distribution among the groups. The mean age among all the groups was comparable (p=0.205). There is no significant gender difference among the three groups (p=0.323).
- Mean FBS (mg/dl) was significantly higher in Micro group (p=0.005) and mean HbA1c was significantly higher in Macro group (p=0.009) .
- Mean SBP (mmHg) was significantly higher in Macro group (p=0.003). Mean DBP (mmHg) was insignificantly higher in Macro group. (p=0.077).
- Mean Serum Creatinine and Urea level were significantly higher in Macro group (p<0.001). eGFR was inversely related and significantly reduced in Macro group (p<0.001).
- With declining renal function i.e. eGFR(cystatin) there is proportional rise in Serum Cystatin C levels which is statistically significant (p<0.001).
- Among the patients who had normal Serum Creatinine (≤1.4 mg/dl), 26.5% have increased Serum Cystatin levels (p<0.001). Among normoalbuminuric patients (n=46), 17.4% patients were having increased Serum Cystatin as compared to 4.3% patients having increased Serum Creatinine which is statistically significant (p<0.001).
- Mean TG, LDL and TC were significantly higher in Macro group compared to Micro and Normo (p<0.001). HDL was comparable between groups (p=0.514).

Table-1: Baseline characteristics of Groups based on Albuminuria

Parameter	Normoalbuminuria	Microalbuminuria	Macroalbuminuria	P value
Age	55.37±8.86	54.27±9.45	55.68±8.77	0.205
FBS	153.35±46.08	184.79±54.04	170.71±50.22	0.005
HbA1c	7.21±1.36	8.04±1.98	8.39±1.25	0.009
SBP	121.91±13.23	125.03±10.71	133.33±12.81	0.003
DBP	76.04±6.49	78.85±8.41	80.24±8.70	0.077
S. Urea	25.57±17.68	38.27±16.09	44.38±12.77	<0.001
S. Creatinine	0.78±0.25	1.24±0.27	1.50±0.74	<0.001
e GFR creatinine	92.39±22.85	64.03±21.43	57.95±29.06	<0.001
S. Cystatin	0.87±0.33	1.26±0.47	2.01±0.95	<0.001
e GFR cystatin	96.04±21.46	63.45±23.25	45.81±20.29	<0.001
HDL	39.78±5.02	38.85±4.28	38.52±4.45	0.514
TG	154.63±47.91	202.82±57.80	230.29±71.22	<0.001
LDL	88.46±20.16	102.82±18.77	108.95±12.24	<0.001
TC	157.00±24.40	183.94±25.45	197.48±24.66	<0.001

Study cohort was also divided based on eGFR (creatinine level). Out of 100 patients, 34% had eGFR <60 whereas 66% had eGFR ≥60.

- Maximum patients belong to age group of 51-60 years in both the groups. (p=0.451). Patients with eGFR <60 have a higher mean age. There is no significant gender difference between two groups. (p =0.189).

- Mean FBS (mg/dl) and mean HbA1c were significantly higher in patients with eGFR <60.
- Mean SBP and DBP was higher in patients with eGFR <60. SBP was comparable between groups (p=0.054) whereas DBP was significantly higher in patients with eGFR<60 compared to eGFR≥60 groups (p=0.015)

- Mean Serum Creatinine and Serum Urea level were significantly higher in patients with eGFR<60.
- Mean Serum cystatin C level was significantly higher in patients with eGFR<60 (1.60±0.81) compared to patients with eGFR≥60 (1.05±0.56) (p=0.001) whereas eGFR (cystatin) was significantly reduced in patients with eGFR (creatinine) <60 (p<0.001).
- In present study, LDL (p=0.013) and TC (p=0.008) were significantly higher in patients with eGFR <60. Mean HDL (p=0.056) and TG (p=0.059) was comparable between both the groups.

Table-2: Baseline characteristics of groups based on eGFR

Parameter	e GFR≥60	e GFR<60	P value
Age (years)	54.67±7.76	57.65±10.31	0.108
FBS (mg/dl)	160.58±46.80	190.38±51.47	0.004
HbA1c (%)	7.44±1.42	8.29±1.89	0.014
SBP	123.55±13.69	128.82±10.88	0.054
DBP	76.52±6.76	80.47±8.97	0.015
S. Creatinine	0.83±0.24	1.58±0.49	<0.001
S.Urea	26.71±12.36	47.29±19.32	<0.001
S. Cystatin	1.05±0.56	1.60±0.81	0.001
e GFR cystatin	89.21±24.13	46.65±17.76	<0.001
HDL	39.85±4.73	37.97±4.30	0.056
TG	177.73±62.75	203.29±64.29	0.059
LDL	93.94±19.90	104.41±18.93	0.013
TC	168.79±28.54	185.26±29.52	0.008

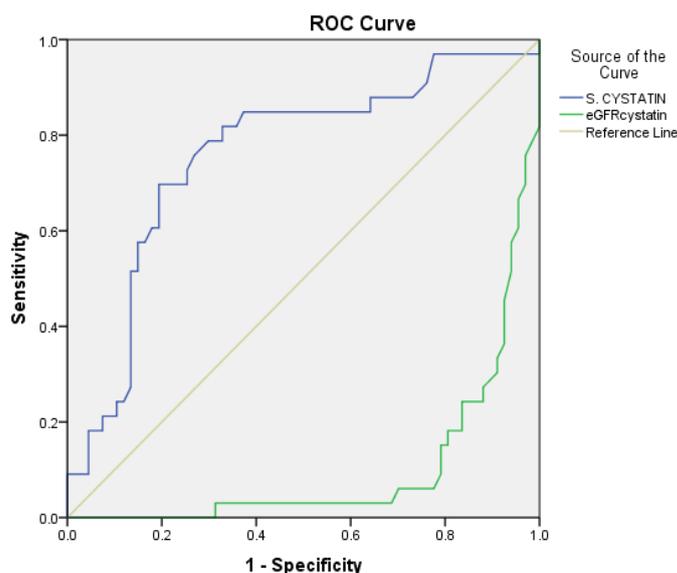
Table-3: Logistic regression for odds ratio

Variables	B	S.E.	Wald	df	P value	odds ratio (EXP(B))	95% C.I.for EXP(B)	
							Lower	Upper
S.CYSTATIN	-3.734	.949	15.488	1	<0.001	.024	.153	
EGFRcystatin	-.204	.046	19.713	1	<0.001	.816	.746	.893
Constant	17.254	3.959	18.992	1	<0.001	31138875.492		

a. Variable(s) entered on step 1: S.CYSTATIN, eGFRcystatin.

The Wald test ("Wald" column) is used to determine statistical significance for each of the independent variables. Logistic regression revealed that Serum Cystatin and e GFR (cystatin) are significant

predictor of outcome i.e nephropathy in given population. The odds ratio of Serum Cystatin is 0.024, that means odds of having nephropathy is 0.024 times greater for patients with increased Serum Cystatin.



In present ROC, Area of Serum Cystatin is 0.758 ($p < 0.001$) which signify that Serum Cystatin can be a fair predictor of nephropathy. Whereas though the eGFR area represent a significant value, area of curve fail to represent nephropathy in study population as the area is just 0.100.

DISCUSSION

The present study entitled “Study of Early Renal Dysfunction in type 2 Diabetics with special reference to Serum Cystatin C levels and Microalbuminuria” was carried out in 100 type 2 Diabetic patients admitted in Medical Wards, Department of Medicine of S.S. Medical College & associated SGMH, Rewa.

In present study mean Serum Cystatin level was significantly higher in Macro (2.01 ± 0.95) compared to Micro (1.26 ± 0.47) and Normo (0.87 ± 0.33) ($p < 0.001$). eGFR(cystatin) was significantly reduced in Macro (45.81 ± 20.29) compared to Micro (63.45 ± 23.25) and Normo (96.04 ± 21.46) ($p < 0.001$). Jeon *et al.* [4] also reported that the Cystatin C levels of serum and urine increased with increasing degree of albuminuria, reaching higher levels in macroalbuminuric patients ($P < 0.001$).

In agreement to present study Takir M *et al.* [5] studied 78 T2DM patients and they divided into 4 groups depending on their urine albumin excretion and eGFR. The values of Cystatin C were significantly increased in the normoalbuminuria group which shows its value as an early marker of Diabetic Nephropathy. Similar findings were reported by Mussap *et al.* [6] who concluded that Cystatin C is a more sensitive marker than Creatinine for the estimation of GFR in type 2 Diabetic patients.

Cross sectional nature was the main limitation of present study; a randomized clinical trial is needed to strengthen the present study findings.

CONCLUSION

In conclusion, the results of this study suggest that Cystatin C measurement in serum is a useful, practical, non-invasive tool for the evaluation of early renal involvement in the course of diabetes, especially in normoalbuminuric patients. With declining renal function i.e. eGFR cystatin there is proportional rise in Serum Cystatin C levels. Hence, Serum Cystatin C may be considered as an early marker, than Microalbuminuria and Serum Creatinine, the commonly used markers for nephropathy in diabetic subjects. With the measurement of the Cystatin C incipient progression of Diabetic renal dysfunction to ESRD can be prevented in most of the patients.

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