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Estimation of serum cystatin c as an early marker of renal dysfunction in type 2 diabetes mellitus

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Abstract

Introduction: Type 2 Diabetes mellitus is the most common metabolic disorder in India. It is assuming epidemic proportions with the Asian-Indian phenotype being more susceptible for the development of the disease. Among Indians, the onset of type 2 diabetes occurs at a younger age making them more vulnerable to develop all the complications of diabetes due to longer duration of the disease.

Aims: To study the utility of serum Cystatin C as a marker for early detection of renal dysfunction in type 2 Diabetes Mellitus.

Materials and Methods: The study included 50 diabetic patients admitted to/ treated on outpatient basis at the Patna Medical College and Hospitals, Patna during the study period extending from May 2021- April 2023.

Result: Glycemic control was assessed by HbA1c. 14 patients (28%) had HbA1c <7% indicating adequate control and 36 (82%) had poorly controlled sugars and 41 patients (82%) all of whom had normal serum creatinine values were found to have 24 hr urine creatinine clearance < 90 mL/min indicating renal dysfunction.

Conclusion: Serum Cystatin C appears to hold promise in predicting early renal dysfunction and more so as an indicator of overt nephropathy. The equation of Rule et al seemed to perform better than Grubb's equation in our study population in estimating GFR.

Keywords: Diabetic nephropathy, Serum cystatin C, Glomerular filtration rate and Meta-analysis

Introduction

Type 2 Diabetes mellitus is the most common metabolic disorder in India. It is assuming epidemic proportions

with the Asian-Indian phenotype being more susceptible for the development of the disease. Among Indians, the onset of type 2 diabetes occurs at a younger age making them more vulnerable to develop all the complications of diabetes dueto longer duration of the disease.

Diabetic nephropathy is currently one of the leading causes of morbidity and mortality in the diabetic population, accounting for the greatest proportion of end stage renal disease worldwide. This microvascular complication is due to a progressive change in the structure and function of the kidney owing to multiple diabetes associated factors. Death rates and rate of renal function decline increases as the disease progresses.

The management of patients with diabetes and end stage renal disease contributes significantly to health care costs. Renal failure in patients with diabetes became a major issue when continuously increasing numbers of diabetic patients were admitted for renal replacement therapy—a veritable medical catastrophe of worldwide dimension. In the past few decades, there have been notable advances in our knowledge regarding the early stagesof diabetic kidney disease, including the advent of interventions that can significantly slow or even reverse the progression of disease. Substantial under-diagnosis of diabetic CKD leads to lost opportunities for prevention, and inadequate or inappropriate care of patients with diabetes and early renal dysfunction.

Previously used parameters to assess renal function include blood urea, serum creatinine and urine albumin estimations. These are known to be influenced by several physiological and pathological factors that render them insensitive or unreliable for early detection of renal dysfunction. It follows that a search has been on for more dependable markers for kidney function. Recently conducted studies have identified Cystatin C as a new, promising and easily measurable marker for prompt detection of early kidney failure. This study was undertaken to evaluate the value of this new molecule in assessing renal dysfunction at a phase when timely interventions can be instituted and the progression of nephropathy delayed.

Materials and methods

Source of data collection

The study included 50 diabetic patients admitted to/ treated on outpatient basis at the Patna Medical College and Hospitals, Patna during the study period extending from May 2021- April 2023.

Inclusion criteria

- Patients with type 2 diabetes mellitus with normal serum creatinine having Creatinine clearance between 90-60 ml/min as determined by the Cockroft and Gault formula were included in the study.

Exclusion criteria

1. Acute coronary syndromes
2. Congestive Heart failure
3. Chronic liver disease
4. Known malignancy
5. Patients on steroids or immunosuppressants
6. Urosepsis

Result and discussion

The present study included 50 participants of which 32 (64%) were males and 18 (36%) were females. 23 (46%) were over the age of 60 yrs. Mean duration of Diabetes was 9.05 yrs.

Glycemic control was assessed by HbA1c. 14 patients (28%) had HbA1c $\leq$7% indicating adequate control and 36 (82%) had poorly controlled sugars.

41 patients (82%) all of whom had normal serum creatinine values were found to have 24 hr urine

creatinine clearance < 90 mL/min indicating renal dysfunction. 27 (54%) of these patients had creatinine clearance in the 60-90 ml/min range indicatingthe target population of early renal function decline. Of these, only 8 patients (29.6%) were on ACE inhibitors or ARBs. Majority of these patients (87.5%) who were on ACE-I or ARB had coexistent hypertension. This probably depicts the large population of diabetics with early renal dysfunction who go undetected and thereby represent lost opportunities for prevention of nephropathy progression. Among patients with nephropathy, 14% had diabetic retinopathy which was less than the literature quoted 60%. [1]The mean serum creatinine was 0.804 mg/dL, ranging from 0.4-1.17 mg/dL (normal reference range for lab 0.4-1.3mg/dL). Creatinine clearance estimated by the Cockroft and Gault equation varied between 60 mL/min and 231 mL/min with a mean of 90.94 mL/min.

Minimum value of Serum Cystatin C by nephelometry was 0.48 ng/L and highest was 1.44 ng/L corresponding to eGFRs of 183 ml/min and 49.08 ml/minusing the following equation:

$$eGFR = 76.6 \times \text{cystatin C [mg/L]}^{-1.16}$$

This equation was originally used in post renal transplant recipients. [2] Using the Grubb's equation it was found that, among this population, eGFR was consistently over-estimated. Previous studies revealed that variables like age, sex and race did have a tendency to influence CysC GFRs in defined settings and in some cases the CysC equations over-estimated the GFR.[3,4] On using the equation proposed by Rule et al, taking readings above a cut off value of Cystatin C of 0.8 mg/L was found to have a better correlation with 24 hr urine creatinine clearance (r=0.43) than Cockroft and Gault estimates(r=0.37). Cystatin C undoubtedly proved to be greater benefit than S. certinine based assay in those patients whose GFR was <60 ml/min consistent with the findings of Yoshiji Ogawa et al. who asserted that CysC was a good predictor of overt nephropathy [5]. Confounding variables of Peripheral Vascular disease and hypothyroidism did not cause statistically significant change in the GFR.

The over estimation of GFR in some subjects despite Rule's equation was thought to represent hyper-filtration which occurs in the early phase of Diabetic nephropathy. However, the anticipated increased 24 hr urine creatinine clearance in this subset was not seen. Two factors might have been confounders in this regard- one, variations in dietary protein intake which was not considered in this study and second, the standardization of Cystatin C kits for the Indian population, as values below reference range were obtained. It is known that significant differences in CysC measurement exist between laboratories using the same assay by the same manufacturer and these lead to clinically relevant abberations in GFR estimation. This interlaboratory variability needs to be recognized when interpreting and comparing CysC and eGFR results. [6]

The only other study in the Indian context did not compare Cys C to standard GFR[7] -a reference database for analyzing our results is lacking. More studies are required to assess whether currently existing data on Cystatin C can directly be extrapolated in our setup.

Conclusion

Serum Cystatin C appears to hold promise in predicting early renal dysfunction and more so as an indicator of overt nephropathy. The equation of Rule et al seemed to perform better than Grubb's equation in our study population in estimating GFR. With a cut off value of ≥ 0.8 mg/L Cystatin C correlated more closely with

standard measure of GFR than Cockroft and Gault assay which is consistent with previous studies.

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Legend Tables

Table 1: Distribution of Comorbid

		No.	%
Comorbid	Hypertension (HTN)	25	50.0
	Peripheral Vascular Disease (PVD)	5	10.0
	Bronchial asthma (ASM)	2	4.0
	Chronic obstructive pulmonary disease (COPD)	3	6.0
	Cerebrovascular Disease (CVD)	2	4.0
	Atrial fibrillation (AF)	1	2.0
	Hypothyroidism (HYPO)	2	4.0
	Migraine	1	2.0
	Seizures (SZ)	1	2.0
	None	8	16.0
	Total	50	100.0
Hb1Ac	<7	14	(28%)
	≥7	36	36 (82%)

Table 2: Association between Confounding variables and GFR

Variable	24hr ClCr	Cys C GFR
PVD* (n=5)	67.4	89
Hypothyroidism** (n=2)	58.0	63.5

Table 3: Type of diabetic retinopathy

Type	NPDR	PDR	Hypertensive
No. (%)	6 (12%)	1 (2%)	6 (12%)