Section: Biochemistry

Original Research Article

STUDY OF SERUM CYSTATIN C AND SERUM CREATININE IN TYPE II DIABETES MELLITUS AS A MARKER OF EARLY DETECTION OF DIABETIC RENAL DISEASE

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Received *: 03/01/2026*
Received in revised form *: 02/02/2026*
Accepted *: 17/02/2026*

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DOI: 10.70034/ijmedph.2026.1.344

Source of Support: Nil,
Conflict of Interest: None declared

Int J Med Pub Health
2026; 16 (1); 1979-1982

ABSTRACT

Background: According to WHO, the prevalence of diabetes is growing most rapidly in low- and middle-income Countries. Chronic kidney disease (CKD) is common, occurring in over 10% of individuals globally, and is increasing in prevalence. The causes of kidney injury are diverse, and the underlying mechanisms are complex. The limitations of traditional biomarkers of renal dysfunction, such as serum creatinine, have been well-demonstrated in the literature. Therefore, augmenting clinical assessment with newer biomarkers, such as serum Cystatin C, has the potential to improve disease monitoring and Patient care. **Aim:** To estimate and compare serum Cystatin C and Serum Creatinine levels in Type II Diabetes Mellitus

Materials and Methods: Type II Diabetes Mellitus Patients aged > 30 years attending the OPD of Medicine Department of Dr. B.R. Ambedkar Medical College and Hospital are estimated for Serum Cystatin C, Serum Creatinine, Fasting blood sugar (FBS) and HbA1C.

Results: In our study we noticed increased Serum Cystatin C levels in 214 (73.18%) out of 290 patients, whereas 26 (9%) patients showed increased Serum Creatinine out of 290 patients. This clearly suggest early rise of Serum Cystatin C compared with creatinine.

Conclusion: Our Study suggests clear elevation in Serum Cystatin C (73.8%) against Serum Creatinine (9%). Cystatin C can be a valuable marker to detect early renal damage. Further study with large population will help to understand role of Cystatin C as a better marker.

Keywords: Cystatin C, Creatinine, Type II Diabetes Mellitus.

INTRODUCTION

Diabetes is a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. Insulin is a hormone that regulates blood sugar. Hyperglycemia, or raised blood sugar, is a common effect of uncontrolled diabetes and over time leads to serious damage to many of the body's systems, especially the nerves and blood vessels.[1]
In India, there are estimated 77 million people above the age of 18 years are suffering from diabetes (type 2) and nearly 25 million are prediabetics (at a higher risk of developing diabetes in near future). More than 50% of people are unaware of their diabetic status which leads to health complications if not detected and treated early. Adults with diabetes have a two- to three-fold increased risk of heart attacks and strokes.[2] Combined with reduced blood flow, neuropathy (nerve damage) in the feet increases the chance of foot ulcers, infection, and the eventual need for limb amputation3. Diabetic retinopathy is an important cause of blindness and occurs as a result of long-term accumulated damage to the small blood

vessels in the retina. Diabetes is among the leading causes of kidney failure.[8]

Diabetic nephropathy (DN), is a major microvascular complication of Diabetes Mellitus, characterized by decrease in GFR,[4,5] and increasing urinary albumin excretion (UAE), starting from microalbuminuria, which progresses to microalbuminuria, macroalbuminuria, and eventually to ESRD. Microalbuminuria is the earliest change of diabetic kidney disease at which appropriate interventions can reduce, or reverse, the disease progression.[6]

Serum creatinine is considered relatively specific but not very sensitive because serum creatinine remains in the normal range until 50% of renal function is lost. This is creatinine blind area. Here GFR range is between 40 - 90ml/min/1.73m^2. Serum creatinine will give false negative results in creatinine blind area. Cystatin C was a good marker of GFR, particularly in patients with early renal impairment.[7]

Cystatin C is a low molecular weight (13 Da) cytoplasmic protein, functioning as an inhibitor of various cysteine protease in the blood stream. Cystatin C has a stable production rate and is removed from the blood circulation by glomerular filtration. In healthy individuals Cystatin C is completely reabsorbed and degraded in the tubules but in subjects with renal disorders its level in blood may be raised as high as 2 to 5 times the normal values. Cystatin C is superior to serum creatinine as a marker of glomerular filtration Rate.

Cystatin C (Cys-C) is a 13-kDa protein which is produced by all nucleated cells. It is not secreted but is fully reabsorbed. 20–40% cases of DM with microalbuminuria develop nephropathy, and most of the patients progressed to end-stage renal disease8. This study has been undertaken to understand the use of Cystatin C over serum creatinine for diagnosis of early renal impairment in Diabetes Mellitus type 2.

The prevention and management of diabetes and associated complications is a huge challenge in India due to several issues and barriers, including lack of multisectoral approach, surveillance data, awareness regarding diabetes, its risk factors and complications, access to health care settings, access to affordable medicines, etc. Thus, effective health promotion and primary prevention, at both individual and population levels are the need of the hour to curb the diabetes epidemic and reduce diabetes-related complications in India.[1]

Diabetes is one of the largest global health emergencies of this century, ranking among the 10 leading causes of mortality together with cardiovascular disease (CVD), respiratory disease, and cancer. According to the World Health Organization (WHO), non-communicable diseases (ncds) accounted for 74% of deaths globally in 2019, of which, diabetes resulted in 1.6 million deaths, thus becoming the ninth leading cause of death globally. By the year 2035, nearly 592 million people are predicted to die of diabetes 10. Type 2 diabetes, which constitutes 90% of all cases of diabetes, earlier considered to be a disease of the affluent "Western" countries, has now spread globally, and has become a major cause of disability and death affecting even younger age group. Diabetes has reached epidemic proportions in many developing economies, such as China and India. According to WHO, the prevalence of diabetes is growing most rapidly in low- and middle-income Countries.[4]

The causes of kidney injury are diverse, and the underlying mechanisms are complex. According to the cause of the disease, kidney injury can be divided into acute kidney injury (AKI) and chronic kidney disease (CKD). The global incidence of AKI in hospitalized patients ranges from 3.0% to 18.3%.[7]

Exclusion Criteria

- Patients with pre-existing renal disease
- Type 1 Diabetes Mellitus
- Any other pre-existing illness likely to affect renal function

Inclusion Criteria

- This study includes Type II Diabetes Mellitus Patients aged >30 years attending the OPD of Medicine Department of DR. B.R. Ambedkar Medical College and Hospital, Bangalore.

MATERIALS AND METHODS

The sample size will consist of 290 Type II Diabetes Mellitus Patients aged >30 years attending the OPD of Medicine Department of DR. B.R Ambedkar Medical College and Hospital.

Cystatin C is estimated by Latex Enhanced Immunoturbidometry method. Reference range of Cystatin C in Serum is 0.56 -1.02 mg/L

Serum Creatinine is estimated by Jaffe's method. Reference range of Serum Creatinine is 0.50 – 1.3 mg/dL.

FBS is estimated by GOD-POD method. Reference range of FBS is 70-110 mg/dL

HbA1c is estimated by HPLC method. Reference range of HBA1c is 4- 6%

Statistical Methods to be Employed

The data is analysed using descriptive statistics tools, 't' test and normal test for proportions used for measuring the statistical significance.

RESULTS

In our study we have found a clear increase in serum Cystatin C levels in 214 (73.8%) out of 290 Patients, 76 subjects had normal serum Cystatin (0.6 – 1.02 mg/L). Whereas, serum Creatinine levels were increased in 26 (9%) subjects out of total 290 and 264 subjects had normal serum Creatinine level.

Statistical analysis clearly indicates elevation of Serum Cystatin C levels in about 73.8% of study population compared with 9% of Serum Creatinine. Cystatin C is elevated in patients where creatinine levels are still in normal range, suggesting Cystatin C as an early marker to detect onset of Renal disease in Type 2 DM.

Table-1 shows descriptive comparison of means of parameters between genders.

Table-2 shows comparison of proportions of abnormality screened by serum Cystatin C and serum Creatinine.

Table 1: Descriptive Comparison of means of parameters between genders

Parameters	Total Mean ± SD	Gender	Number of Patients (N=290)	Min	Max	Mean ± SD	P value
Age in years	53.4 ± 12.7	Female	162	30	80	51.8 ± 12.8	0.018*
		Male	128	30	86	55.3 ± 12.4	
HbA1C (4-6%)	8.7 ± 2.5	Female	162	4.9	15.2	8.2 ± 2.5	0.050*
		Male	128	4.6	15.9	8.8 ± 2.5	
Estimated Average Blood Glucose (70- 130 mg/ dL)	196.0 ± 71.8	Female	162	93	389.6	188.7 ± 70.4	0.050*
		Male	128	85.3	409.6	205.3 ± 72.9	
Fasting Blood Sugar (70-110mg/dL)	148.9 ± 71.3	Female	162	76	433	150.3 ± 71.2	0.706
		Male	128	76	433	147.1 ± 71.6	
		Male	128	1.8	24	10.6 ± 5.2	
Serum Cystatin-C (0.6-1.02mg/L)	1.06 ± 0.1	Female	162	0.9	1.3	1.05 ± 0.1	0.398
		Male	128	0.9	1.3	1.06 ± 0.1	
Serum Creatinine (0.5-1.3 mg/dl)	1.03 ± 0.6	Female	162	0.6	0.6	1.02 ± 0.55	0.880
		Male	128	4.5	4.5	1.03 ± 0.57	

Table 2: Comparison of Proportion of abnormality screened by Serum Cystatin-c and Serum Creatinine

Parameters	No. Patients (n=290)			
	Normal	Percentage	Abnormal	Percentage
Serum Cystatin-C (0.56 -1.02mg/L)	76	26.2	214	73.8
Serum Creatinine (0.5-1.3 mg/dl)	264	91.0	26	9.0
Total	290 100		290 100	
P-Value	0.0001**		0.0001**	

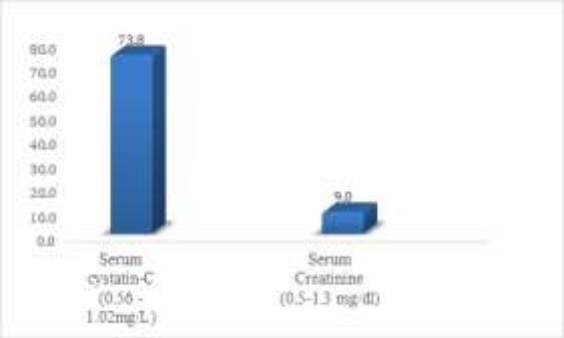

Figure 1: Pictorial representation of Percentage of abnormality of Type -2 Diabetes Milletus by Serum Cystatin C and Serum Creatinine

DISCUSSION

Our study suggests a clear increase in Serum Cystatin C levels (1.06 ± 0.1 mg/L) as a whole and around 214 patients (73.8%) showed high value and 76 had normal values. Serum Creatinine level is 1.03 ± 0.6 mg/dL as a whole, which is normal range, and 26 patients that is (9%) showed elevated serum Creatinine levels.

76 subjects of Cystatin C levels were in normal range whereas serum Creatinine was found to be increased in 26 out of 290 Patients and 264 Patients' creatinine levels were in normal range.

The statistical analysis of the study clearly highlights the early rise in serum Cystatin C level in 73.8% Patients and 9% Patients only showed elevated Creatinine levels. This result clearly suggests serum Cystatin C as an early marker to indicate onset of nephropathy in Type II Diabetes Patients.

Diabetic Nephropathy is one of the complications of Diabetes Mellitus and is considered to be one of the leading causes of end-stage renal failure.[12] The clinical markers currently used to diagnose Diabetic Nephropathy are serum Creatinine, urea and endogenous Creatinine clearance rates. But these indicators are easily affected by a number of extra-renal factors, like age, gender, height, muscle mass, diet, body disease conditions and drugs. Therefore, these indicators are not ideal markers of Diabetic Nephropathy.

Our study is in agreement with Abrahamson. M et al. Cystatin C is a kidney filtration marker that, when used in combination with serum Creatinine, provides a more precise estimate of glomerular filtration rate (EGFR) than using serum Creatinine alone. Major kidney organizations, including the National Kidney Foundation, the American Society of Nephrology and the kidney disease: Improving Global Outcomes have urged incorporation of Cystatin C testing in routine clinical care. Despite these recommendations, prevalence of Cystatin C testing is low and many Clinicians are unfamiliar with the assay.[8]

Cystatin C (CYSC) is a good marker that reflects glomerular dysfunction faster and is more sensitive than Creatinine. CYSC can be freely filtered by the

kidney, reabsorbed, and degraded in the proximal convoluted tubule of the glomerulus. Moreover, CYSC is not excreted by the kidney tubule. CYSC can meet the requirements of ideal endogenous GFR markers and is a new sensitive index for evaluating GFR Some of the most important findings about Cystatin C are in the area of renal disease.[7] Vijay et al. Demonstrated that there was an increased urine Cys C level in T2DM with early diabetic nephropathy as compared to patients without nephropathy, and the increase of Cys C level was positively correlated with microalbuminuria

Zhanget al. Reported that serum Cys C was more sensitive than serum creatinine for estimation of GFR in T2DM.[5]

Cys C is a good marker of incipient renal disease and represents an ideal endogenous index reflecting the GFR. Serum Cys C could be a more precise indicator than serum creatinine because it is less affected by other factors, thereby reflecting renal function much more precisely in early renal function lesions of T2DM.[6]

Since Cys C is more reliable for assessment of renal function, it is also a potential indicator and has an associative relationship with the CV risk prediction of diabetes patients. A recent study that included 523 T2DM patients revealed that, compared to the T2DM with non-subclinical atherosclerosis group, there was an increased serum Cys C level in the subclinical atherosclerosis group, and the concentration of Cys C was correlated with brachial-ankle pulse wave velocity, suggesting a potential role of Cys C in predicting arterial stiffness. Other studies have also found an association of serum Cys C with vascular complications, carotid arterial wall elasticity and subclinical atherosclerosis in T2DM.[8]

A study by Vaduganathan et al. Revealed that the renal biomarker of Cys C was independently associated with subsequent cardiovascular (CV) risk. Moreover, there was a positive association of serum Cys C with CV autonomic neuropathy in patients with T2DM. Those studies suggested the important role of Cys C involved in Type 2 DM with CV complications.[9]

Cystatin C is a kidney filtration marker that, when used in combination with serum creatinine, provides a more precise estimate of glomerular filtration rate (EGFR) than using serum creatinine alone. Cystatin C (CYSC) is a good marker that reflects glomerular dysfunction faster and is more sensitive than Creatinine3. CYSC can be freely filtered by the kidney, reabsorbed, and degraded in the proximal convoluted tubule of the glomerulus. Moreover, CYSC is not excreted by the kidney tubule. CYSC can meet the requirements of ideal endogenous GFR markers and is a new sensitive index for evaluating GFR.[9]

Cystatin C to be an emerging endogenous marker for quick and accurate assessment of renal function.

We have decided to review elaborately on Cystatin C as a marker of renal function and to review the sensitivity and specificity of cystatin C as an endogenous marker compared to serum creatinine.[10]

CONCLUSION

Our study clearly suggests elevation of Serum Cystatin C levels in 73.8% of patients compared to only 9% elevation of Serum Creatinine. This suggests Cystatin 'C' to be early marker than Creatinine to assess renal involvement in Type 2 DM. Further study with large population will help to understand role of Cystatin C as a better marker.

Conflict of interest: The study has no conflict of interest to declare.

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