The Review Of
DIABETIC
STUDIES OPEN ACCESS

Comparative Evaluation Of Serum Creatinine, Cystatin C, And Albuminuria For Early Renal Dysfunction In Type 2 Diabetes: A Cross-Sectional Study

Dr. Manpreet Saini[1], Dr. Vijay Kumar[2]*, Dr. Ajit Thakur[3]

[1] Associate Professor, Department of Biochemistry, Laxmi Chandravansi Medical College and Hospital, Palamu, India
[2] Professor, Department of Community Medicine, Laxmi Chandravansi Medical College and Hospital, Palamu, India
[3] Associate Professor, Department of Biochemistry, V.C.S.G.G.I.M.S.&R., Srinagar, Garhwal, India
**Corresponding Author: Dr. Vijay Kumar, Professor, Department of Community Medicine, Laxmi Chandravansi Medical College and Hospital, Palamu, India.*

Abstract-

Introduction- Type 2 diabetes mellitus frequently leads to diabetic kidney disease, a major cause of chronic kidney disease and cardiovascular morbidity. Early detection remains challenging due to limitations of serum creatinine and albuminuria. Cystatin C has emerged as a potentially more sensitive biomarker. This study comparatively evaluates these markers for early renal dysfunction detection.
Material and Method- This cross-sectional study included 90 adults with type 2 diabetes. Patients with advanced kidney disease were excluded. Serum creatinine, cystatin C, HbA1c, estimated glomerular filtration rate (eGFR), and urine albumin-to-creatinine ratio (ACR) were measured. Early renal dysfunction was defined as eGFR 60–89 mL/min/1.73m² and/or microalbuminuria. Statistical analysis was performed using SPSS.
Result- Among 90 patients with type 2 diabetes (mean age 52.4±7.8 years), 80% had microalbuminuria despite preserved eGFR. Serum cystatin C was significantly higher in microalbuminuria and showed stronger correlations with ACR and eGFR than creatinine. ROC analysis demonstrated superior diagnostic accuracy for cystatin C (AUC 0.84). Multivariate analysis identified cystatin C, diabetes duration, and HbA1c as independent predictors of microalbuminuria.
Conclusion- Serum cystatin C demonstrated superior diagnostic accuracy compared to creatinine for early renal dysfunction in type 2 diabetes. Its strong association with microalbuminuria supports its role as a sensitive biomarker for early detection and improved risk stratification in diabetic kidney disease.

Keywords- Type 2 diabetes mellitus, Cystatin C, Serum creatinine, Microalbuminuria, Early renal dysfunction, eGFR etc.

Introduction-

Type 2 diabetes mellitus (T2DM) is a major global health concern, with its prevalence increasing rapidly across both developed and developing countries. The International Diabetes Federation estimates that diabetes affects hundreds of millions worldwide, and this number is projected to rise substantially in the coming decades [1]. Among the various microvascular complications, diabetic kidney disease (DKD) remains one of the most serious, contributing significantly to chronic kidney disease (CKD), end-stage renal disease (ESRD), and cardiovascular morbidity and mortality [2]. Approximately 30–50% of individuals with T2DM are expected to develop some degree of renal impairment during their lifetime [3]. Early detection of renal dysfunction is therefore crucial to delay disease progression and reduce associated complications. Traditionally, renal function assessment in T2DM relies on serum creatinine-based

estimated glomerular filtration rate (eGFR) and measurement of urinary albumin excretion, typically expressed as albumin-to-creatinine ratio (ACR). Persistent albuminuria is considered an early marker of diabetic nephropathy and is recommended for routine screening [4,5]. However, serum creatinine has well-recognized limitations. It is influenced by age, gender, muscle mass, and dietary intake, and significant nephron loss may occur before creatinine levels rise above the normal range [6]. Moreover, emerging evidence highlights the presence of non-albuminuric diabetic kidney disease, suggesting that albuminuria alone may not detect all cases of early renal dysfunction [7].

Cystatin C, a low molecular weight protein produced by all nucleated cells and freely filtered at the glomerulus, has gained attention as a potentially more sensitive biomarker of early renal impairment. Unlike creatinine, cystatin C levels are less affected by muscle mass and other extrarenal factors [8]. Several studies have demonstrated that serum cystatin C may detect early reductions in GFR even before changes in creatinine or overt albuminuria become evident [9,10]. Its use either alone or in combination with creatinine has shown improved accuracy in identifying early CKD stages in diabetic populations. Despite growing evidence supporting cystatin C, there remains uncertainty regarding its comparative utility alongside conventional markers such as serum creatinine and albuminuria, particularly in resource-limited settings. Furthermore, variability in findings across populations necessitates context-specific evaluation. Therefore, the present study aims to comparatively evaluate serum creatinine, serum cystatin C, and albuminuria in the detection of early renal dysfunction among patients with T2DM. Establishing the most reliable early marker may enhance screening strategies, facilitate timely intervention, and ultimately reduce the burden of diabetic kidney disease.

Material and Method-

This cross-sectional study was conducted from September 2024 to March 2025 in a tertiary care centre of Jharkhand, India. The study protocol was approved by the Institutional Ethics Committee. Patients diagnosed with Type 2 Diabetes Mellitus (T2DM) attending outpatient and inpatient services were screened during the study period. A total of 90 patients with confirmed T2DM were included in the study. Participants were recruited consecutively during the study period after applying predefined inclusion and exclusion criteria. Patients aged between 30 and 70 years with T2DM of at least one year duration were included. Only patients fulfilling the standard diagnostic criteria for T2DM were enrolled for final analysis. Type 2 Diabetes Mellitus was confirmed based on the American Diabetes Association (ADA) diagnostic criteria. Patients were considered to have T2DM if they fulfilled any of the following: fasting plasma glucose ≥126 mg/dL, 2-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test, glycated hemoglobin (HbA1c) ≥6.5%, or random plasma glucose ≥200 mg/dL in the presence of classic symptoms of hyperglycemia. Previously diagnosed cases receiving antidiabetic treatment were also included after verification of medical records. Differentiation from Type 1 Diabetes Mellitus was based on age at onset, clinical history, requirement of lifelong insulin from diagnosis, and physician documentation.

Individuals with previously diagnosed chronic kidney disease (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m²), macroalbuminuria (albumin-to-creatinine ratio >300 mg/g), acute kidney injury, pregnancy, active infection, thyroid dysfunction, malignancy, chronic liver disease, or those on nephrotoxic medications were excluded to avoid confounding effects on renal biomarkers. After obtaining written informed consent, demographic and clinical details including age, sex, duration of diabetes, and treatment history were recorded using a structured proforma. Body mass index (BMI) was calculated using the formula weight (kg) / height (m²). Five milliliters of fasting venous blood was collected under aseptic precautions. Blood glucose and serum creatinine (S. Creatinine) were estimated on an auto-analyzer – Roche Cobas 6000 system (c501) using enzymatic method. HbA1c was assessed using Bio-Rad D-10 which uses the principle of Ion Exchange High Performance Liquid Chromatography (HPLC). Serum cystatin C (S. cystatin C) was measured using a particle-enhanced immunoturbidimetric assay. Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI creatinine-based equation. A spot midstream urine sample was collected for estimation of urinary albumin and urinary creatinine, and the albumin-to-creatinine ratio (ACR) was calculated. Early renal dysfunction was defined as eGFR between 60–89

mL/min/1.73 m² and/or presence of microalbuminuria (ACR 30–300 mg/g). Data were entered into Microsoft Excel and subsequently imported into SPSS software version 15 for statistical analysis. Continuous variables were expressed as mean ± standard deviation, while categorical variables were presented as frequencies and percentages. Appropriate statistical tests were applied for comparison and correlation analysis. A p-value <0.05 was considered statistically significant.

Result-

A total of 90 patients with type 2 diabetes mellitus were included in the study. Among them, 58 (64.4%) were males and 32 (35.6%) were females, indicating a male predominance in the study population. The mean age of the participants was 52.4 ± 7.8 years (range: 35–68 years). As seen in Figure 1, age-wise distribution of the study participants revealed that the majority belonged to the 40–59 years age group, comprising 63 individuals (70.0%). Participants aged ≥60 years accounted for 21 cases (23.3%), while only 6 participants (6.7%) were in the 30–39 years age group.

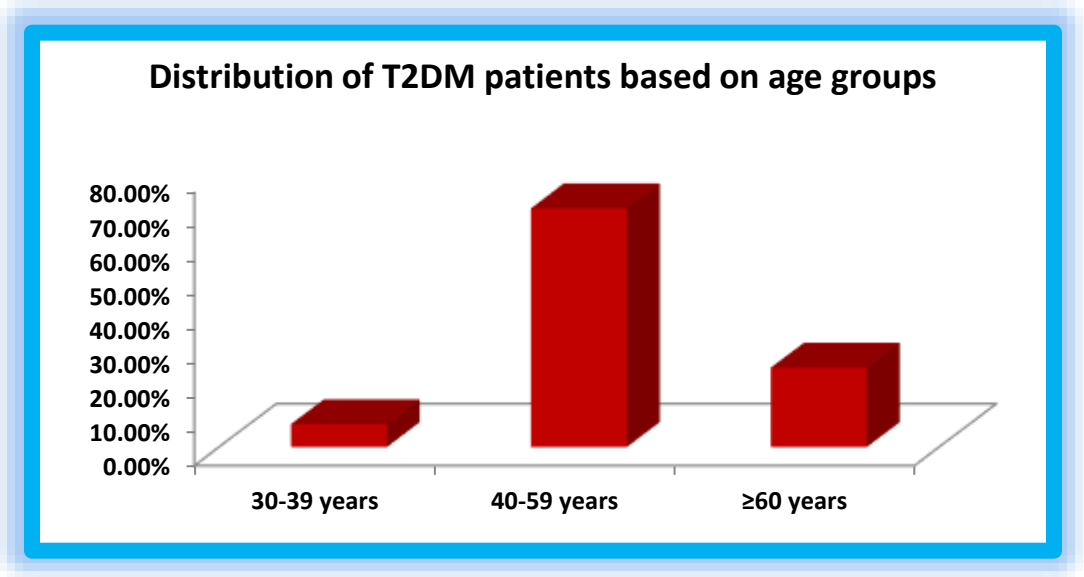

Figure 1- Distribution of T2DM patients based on age groups

As shown in table 1, the study population was predominantly overweight, with a mean BMI of 27.8 ± 3.4 kg/m². The mean duration of diabetes was 7.6 ± 3.8 years, ranging from 2 to 18 years as clear in Table 1. Glycemic parameters indicated suboptimal metabolic control, with a mean fasting blood sugar of 178.3 ± 42.5 mg/dL and postprandial blood sugar of 248.7 ± 61.2 mg/dL. The mean HbA1c was 8.6 ± 1.4%, reflecting poor long-term glycemic control among participants. Regarding renal parameters, the mean serum creatinine level was 1.08 ± 0.24 mg/dL, while the mean serum cystatin C level was 1.42 ± 0.31 mg/L. The mean estimated glomerular filtration rate (eGFR) was 82.6 ± 11.4 mL/min/1.73m², indicating predominantly early-stage renal dysfunction. The mean urine albumin-to-creatinine ratio (ACR) was 146.5 ± 62.8 mg/g, with values ranging from 35 to 295 mg/g, suggesting a high prevalence of early renal involvement. Overall, the baseline characteristics reflect a middle-aged diabetic population with moderate disease duration, inadequate glycemic control, and evidence of early renal impairment.

Table 1- Baseline demographic and biochemical characteristics of study participants

Parameter	Mean ± SD	Range
Age (years)	52.4 ± 7.8	35–68
BMI (kg/m²)	27.8 ± 3.4	21.5–34.9
Duration of Diabetes (years)	7.6 ± 3.8	2–18

Fasting Blood Sugar (mg/dL)	178.3 ± 42.5	110–280
Postprandial Blood Sugar (mg/dL)	248.7 ± 61.2	160–390
HbA1c (%)	8.6 ± 1.4	6.2–12.4
Serum Creatinine (mg/dL)	1.08 ± 0.24	0.7–1.6
Serum Cystatin C (mg/L)	1.42 ± 0.31	0.9–2.1
eGFR (mL/min/1.73m²)	82.6 ± 11.4	62–108
Urine ACR (mg/g)	146.5 ± 62.8	35–295

The distribution of albuminuria categories seen in Figure 2, revealed that the majority of participants had microalbuminuria. Out of 90 patients, 72 (80.0%) were classified as having microalbuminuria (ACR 30–300 mg/g), while 18 (20.0%) had normoalbuminuria (ACR <30 mg/g). This distribution indicates a high prevalence of early renal involvement among patients with type 2 diabetes in the study. The predominance of microalbuminuria highlights the presence of subclinical renal dysfunction despite relatively preserved eGFR in many participants, emphasizing the importance of sensitive biomarkers for early detection.

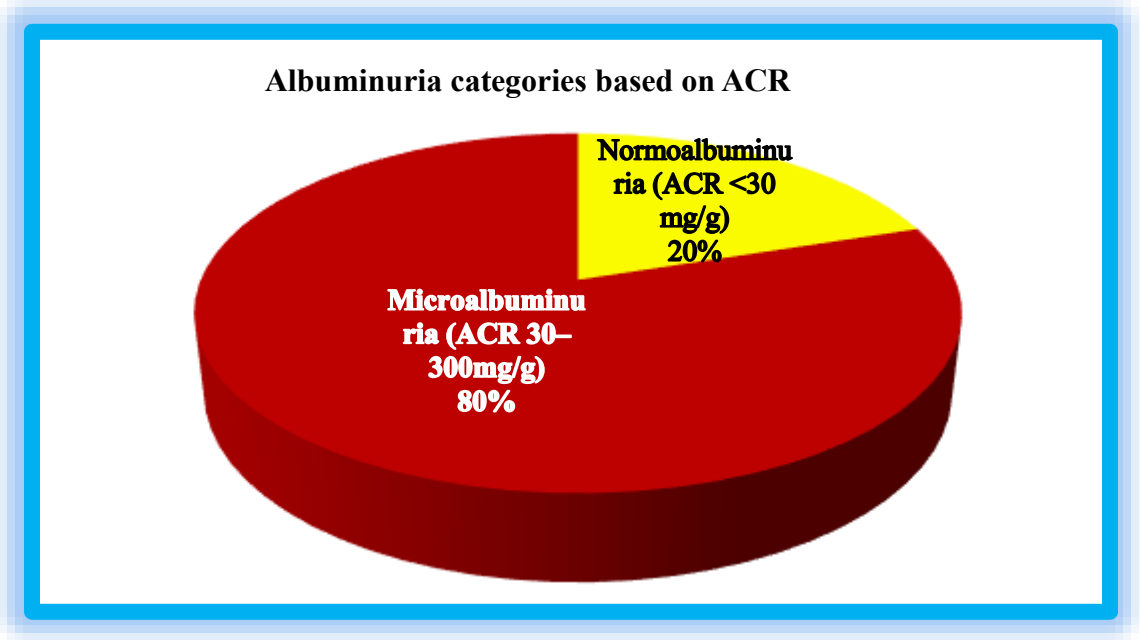

Figure 2- Albuminuria categories based on ACR

Table 2 shows that on subgroup analysis, 18 participants (20.0%) had normoalbuminuria, while 72 (80.0%) had microalbuminuria. A statistically significant difference was observed between the two groups across multiple clinical and renal parameters. As expected, the mean urine ACR was significantly higher in the microalbuminuria group (172.3 ± 58.7 mg/g) compared to the normoalbuminuria group (18.6 ± 6.4 mg/g) ($p < 0.001$). Serum creatinine levels were modestly but significantly elevated in participants with microalbuminuria (1.11 ± 0.25 mg/dL) compared to those with normoalbuminuria (0.98 ± 0.18 mg/dL) ($p = 0.041$). In contrast, serum cystatin C demonstrated a more pronounced difference between the groups, with significantly higher levels in the microalbuminuria group (1.50 ± 0.28 mg/L) compared to the normoalbuminuria group (1.09 ± 0.21 mg/L) ($p < 0.001$). Similarly, mean eGFR was significantly lower among patients with microalbuminuria (79.8 ± 10.9 mL/min/1.73m²) than those with normoalbuminuria (91.3 ± 8.6 mL/min/1.73m²) ($p < 0.001$), indicating early decline in renal function. Additionally, the duration of diabetes was significantly longer in the microalbuminuria group (8.1 ± 3.9 years) compared to the normoalbuminuria group (5.4 ± 2.1 years) ($p = 0.003$). Overall, these findings suggest that patients with microalbuminuria had significantly higher cystatin C levels, mild but significant elevations in creatinine,

reduced eGFR, and longer diabetes duration, highlighting the association of cystatin C with early renal dysfunction.

Table 2- Comparison between normoalbuminuria and microalbuminuria

Parameter	Normoalbuminuria (n = 18)	Microalbuminuria (n = 72)	p-value
Urine ACR (mg/g)	18.6 ± 6.4	172.3 ± 58.7	**<0.001**
Serum Creatinine (mg/dL)	0.98 ± 0.18	1.11 ± 0.25	**0.041**
Serum Cystatin C (mg/L)	1.09 ± 0.21	1.50 ± 0.28	**<0.001**
eGFR (mL/min/1.73m²)	91.3 ± 8.6	79.8 ± 10.9	**<0.001**
Duration of Diabetes (years)	5.4 ± 2.1	8.1 ± 3.9	**0.003**

Correlation analysis depicted in Table 3, demonstrated significant associations between renal biomarkers and clinical parameters, with serum cystatin C consistently showing stronger correlations compared to serum creatinine. Serum creatinine showed a moderate positive correlation with urine ACR ($r = 0.38$, $p = 0.010$) and a significant negative correlation with eGFR ($r = –0.54$, $p < 0.001$). It also demonstrated a weak positive correlation with duration of diabetes ($r = 0.29$, $p = 0.040$). However, its correlation with HbA1c did not reach statistical significance ($r = 0.25$, $p = 0.060$). In comparison, serum cystatin C exhibited a stronger positive correlation with urine ACR ($r = 0.61$, $p < 0.001$) and a stronger negative correlation with eGFR ($r = –0.68$, $p < 0.001$). Additionally, cystatin C showed a significant positive correlation with duration of diabetes ($r = 0.44$, $p = 0.002$) and HbA1c ($r = 0.39$, $p = 0.010$). Overall, cystatin C demonstrated stronger and more consistent correlations with markers of renal dysfunction and glycemic control compared to serum creatinine, supporting its potential role as a more sensitive biomarker for early renal impairment in type 2 diabetes.

Table 3- Comparative correlation analysis of serum creatinine and cystatin C with clinical and renal parameters

Variable	Creatinine (r)	p-value	Cystatin C (r)	p-value
Urine ACR	0.38	**0.010**	0.61	**<0.001**
eGFR	-0.54	**<0.001**	-0.68	**<0.001**
Duration of Diabetes	0.29	**0.040**	0.44	**0.002**
HbA1c	0.25	0.060	0.39	**0.010**

Table 4 illustrates that receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of S. creatinine, S. cystatin C, and eGFR in detecting early renal dysfunction (microalbuminuria). S. cystatin C demonstrated the highest diagnostic accuracy, with an area under the curve (AUC) of 0.84 (95% CI: 0.76–0.92), indicating good discriminatory ability. At a cut-off value of 1.32 mg/L, cystatin C showed a sensitivity of 82% and specificity of 79% for detecting microalbuminuria. In comparison, serum creatinine showed lower diagnostic performance, with an AUC of 0.64, reflecting modest discrimination. At a cut-off of 1.1 mg/dL, creatinine demonstrated 58% sensitivity and 62% specificity. The AUC for eGFR was 0.71, indicating fair diagnostic accuracy. At a cut-off value of 85 mL/min/1.73m², eGFR had a sensitivity of 69% and specificity of 68%. Overall, S. cystatin C outperformed both S. creatinine and eGFR in identifying early renal dysfunction, demonstrating superior sensitivity, specificity, and overall diagnostic accuracy.

Table 4- ROC curve analysis to assess diagnostic performance for detecting early renal dysfunction (microalbuminuria)

Parameter	AUC (95% CI)	Sensitivity (%)	Specificity (%)	Cut-off
S. Creatinine	0.64 (0.54–0.74)	58	62	1.1 mg/dL
S. Cystatin C	0.84 (0.76–0.92)	82	79	1.32 mg/L
eGFR	0.71 (0.61–0.81)	69	68	85 mL/min

Multivariate regression analysis was performed to identify independent predictors of microalbuminuria after adjusting for relevant clinical variables as clear in Table 5. Serum cystatin C emerged as a significant independent predictor of microalbuminuria ($\beta = 0.49$, $p < 0.001$), demonstrating the strongest association among all variables included in the model. Duration of diabetes ($\beta = 0.27$, $p = 0.02$) and HbA1c ($\beta = 0.21$, $p = 0.04$) were also independently associated with microalbuminuria, indicating that longer disease duration and poor glycemic control contribute significantly to early renal dysfunction. In contrast, serum creatinine did not retain statistical significance in the multivariate model ($\beta = 0.18$, $p = 0.09$). Similarly, hypertension showed a positive but non-significant association ($\beta = 0.16$, $p = 0.08$). Overall, these findings indicate that serum cystatin C is an independent and stronger predictor of early renal dysfunction compared to serum creatinine, even after adjusting for glycemic control, duration of diabetes, and hypertension.

Table 5- Multivariate regression analysis for predictors of microalbuminuria

Variable	Beta Coefficient	p-value
Serum Creatinine	0.18	0.09
Serum Cystatin C	0.49	**<0.001**
Duration of Diabetes	0.27	**0.02**
HbA1c	0.21	**0.04**
Hypertension	0.16	0.08

Discussion-

The present study evaluated the comparative performance of serum creatinine, serum cystatin C, and albuminuria in detecting early renal dysfunction among patients with type 2 diabetes mellitus (T2DM). Despite preserved or mildly reduced eGFR in all participants, a high prevalence (80%) of microalbuminuria was observed, highlighting substantial subclinical renal involvement. This finding is consistent with reports indicating that early diabetic kidney disease (DKD) frequently develops even when conventional renal function parameters appear relatively preserved [11]. A key finding of our study was that serum cystatin C levels were significantly higher in patients with microalbuminuria compared to those with normoalbuminuria, with a more pronounced difference than observed for serum creatinine. This result is supported by the study of Asmamaw et al. [12], who demonstrated that cystatin C levels rise earlier than creatinine in T2DM patients with early nephropathy. Similarly, Sapkota et al. [13] reported superior sensitivity of cystatin C in identifying early renal impairment. In contrast, some earlier investigations suggested only marginal superiority of cystatin C over creatinine in certain diabetic populations, indicating that population characteristics may influence biomarker performance [14]. Correlation analysis in our study further strengthened the role of cystatin C. It showed stronger positive correlation with urine ACR and stronger negative correlation with eGFR compared to creatinine. Additionally, cystatin C correlated significantly with duration of diabetes and HbA1c, whereas creatinine did not show a significant association with glycemic control. These findings are supported by Kim et al. [15], who observed that cystatin C correlates more closely with measured GFR and metabolic parameters in T2DM. However, in contrast, Jeon et al. [14] reported comparable correlations between creatinine and cystatin C in certain subgroups, suggesting variability based on study design and baseline renal function.

Importantly, ROC curve analysis in our study demonstrated that cystatin C had the highest diagnostic accuracy (AUC 0.84) compared to creatinine (AUC 0.64) and eGFR (AUC 0.71). This superior discriminatory ability aligns with findings by Bjornstad et al. [16], who emphasized that cystatin C–based

assessment improves early detection of diabetic kidney disease. In contrast, reliance solely on creatinine-based eGFR may delay diagnosis because serum creatinine levels rise only after substantial nephron loss [11]. Multivariate regression analysis identified serum cystatin C as an independent predictor of microalbuminuria, even after adjusting for duration of diabetes, HbA1c, and hypertension. Duration of diabetes and poor glycemic control also independently predicted early renal dysfunction, consistent with established pathophysiological mechanisms [2,17]. The lack of independent significance of serum creatinine in our study underscores its limited sensitivity in early disease stages. These findings are supported by Inker et al. [11], who reported improved risk stratification when cystatin C is incorporated into renal assessment models. Overall, our findings reinforce the growing body of evidence suggesting that cystatin C is a more sensitive and reliable biomarker than serum creatinine for detecting early renal dysfunction in T2DM. Given the high prevalence of microalbuminuria observed despite preserved eGFR, combining cystatin C with albuminuria assessment may enhance early diagnosis, enable timely therapeutic intervention, and potentially reduce progression to advanced DKD.

Conclusion-

The present study demonstrates that serum cystatin C is a superior biomarker compared to serum creatinine for the early detection of renal dysfunction in patients with type 2 diabetes mellitus. While albuminuria remains an established marker of early diabetic kidney disease, our findings indicate that cystatin C provides greater diagnostic accuracy, higher sensitivity and specificity, and stronger correlation with estimated glomerular filtration rate. Unlike creatinine, which may remain within normal limits until significant nephron loss occurs, cystatin C appears to detect subtle reductions in renal function at an earlier stage. Furthermore, its independent association with microalbuminuria highlights its potential role in identifying patients at increased risk of progressive renal impairment. Early identification of renal dysfunction in type 2 diabetes enables timely initiation of renoprotective strategies, optimization of glycemic and blood pressure control, and prevention of long-term complications. Incorporating serum cystatin C into routine assessment alongside albuminuria and eGFR may improve risk stratification and patient outcomes. Future large-scale, longitudinal studies are warranted to validate these findings and support the integration of cystatin C into standard diabetic kidney disease screening protocols.

Source of Funding- Nil.

Conflicts of Interest- None

References-

1. International Diabetes Federation. IDF Diabetes Atlas. 10th ed. Brussels: IDF; 2021.
2. Alicic RZ, Rooney MT, Tuttle KR. Diabetic kidney disease: challenges, progress, and possibilities. Clin J Am Soc Nephrol. 2017;12(12):2032-2045.
3. Thomas MC, Brownlee M, Susztak K, et al. Diabetic kidney disease. Nat Rev Dis Primers. 2015;1:15018.
4. American Diabetes Association. Chronic kidney disease and risk management: Standards of Care in Diabetes—2024. Diabetes Care. 2024;47(Suppl 1):S219-S230.
5. KDIGO 2022 Clinical Practice Guideline for Diabetes Management in CKD. Kidney Int. 2022;102(5S):S1-S127.
6. Baxmann AC, Ahmed MS, Marques NC, Menon VB, Pereira AB, Kirsztajn GM, Heilberg IP. Influence of muscle mass and physical activity on serum and urinary creatinine and serum cystatin C. Clin J Am Soc Nephrol. 2008 Mar;3(2):348-54. doi: 10.2215/CJN.02870707. Epub 2008 Jan 30. PMID: 18235143; PMCID: PMC2390952.
7. Penno G, Solini A, Bonora E, et al. Non-albuminuric renal impairment in type 2 diabetes. Diabetes Care. 2015;38(6):1069-1077.

8. Shlipak MG, Mattes MD, Peralta CA. Update on cystatin C: incorporation into clinical practice. Am J Kidney Dis. 2013;62(3):595-603.
9. Dharnidharka VR, Kwon C, Stevens G. Serum cystatin C is superior to serum creatinine as a marker of kidney function. Am J Kidney Dis. 2015;65(1):40-47.
10. Jeon YK, Kim MR, Huh JE, et al. Cystatin C as an early biomarker of nephropathy in patients with type 2 diabetes. Diabetes Metab J. 2016;40(1):60-68.
11. Inker LA, Schmid CH, Tighiouart H, et al. Estimating glomerular filtration rate using serum creatinine and cystatin C. N Engl J Med. 2015;372:20–29.
12. Asmamaw T, et al. Early detection of renal impairment among patients with type 2 diabetes mellitus through evaluation of serum cystatin C in comparison with serum creatinine levels. Diabetes Metab Syndr Obes. 2020;13:4721–4728.
13. Sapkota S, Khatiwada S, Shrestha S, et al. Diagnostic accuracy of serum cystatin C for early recognition of nephropathy in type 2 diabetes mellitus. Int J Nephrol. 2021;2021:8884126.
14. Jeon YL, Kim MH, Lee WI, et al. Cystatin C as an early marker of diabetic nephropathy in patients with type 2 diabetes. Clin Lab. 2015;61(11-12):1665–1671.
15. Kim SS, Song SH, Kim IJ, et al. Clinical significance of cystatin C-based estimates of renal function in patients with type 2 diabetes. Diabetes Metab J. 2018;42(3):233–242.
16. Bjornstad P, Maahs DM, Cherney DZ. Cystatin C as a biomarker of diabetic kidney disease. Kidney Int. 2015;87(4):750–757.
17. MacIsaac RJ, Jerums G, Ekinci EI. Effects of glycaemic management on diabetic kidney disease. World J Diabetes. 2017 May 15;8(5):172-186. doi: 10.4239/wjd.v8.i5.172. PMID: 28572879; PMCID: PMC5437616.