ISSN: 2320-9267

Indian Journal of Pharmaceutical and Biological Research (IJPBR)

Journal homepage: www.ijpbr.in

RESEARCH ARTICLE

Comparison of Creatinine and Cystatin C-based Estimated Glomerular Filtration Rate in Relation to Glycemic Control Among Patients With Type 2 Diabetes Mellitus

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ABSTRACT

Background & Objectives: Diabetic kidney disease (DKD) is a major complication of type 2 diabetes mellitus (T2DM) leading to end-stage renal disease (ESRD). Early identification of declining renal function is vital to prevent disease progression. Estimated glomerular filtration rate (eGFR) calculated using serum creatinine or serum cystatin C serves as a key indicator of kidney function. This study aimed to compare creatinine-based (MDRD equation) and cystatin C-based (CKD-EPI 2012 equation) eGFR in relation to glycemic control (HbA1c) in patients with type 2 diabetes mellitus and healthy controls.

Materials & Methods: This cross-sectional case–control study included 150 participants aged 25–70 years, comprising 75 clinically diagnosed T2DM patients (cases) and 75 apparently healthy individuals (controls). Patients with hypertension, known chronic kidney disease, hepatic/muscular disorders, or those undergoing dialysis were excluded. Serum creatinine (enzymatic method) and serum cystatin C (immunoturbidimetric assay) were analyzed on a Beckman AU5800 clinical chemistry analyzer. Glycated hemoglobin (HbA1c) was measured by high-performance liquid chromatography (HPLC). eGFR was calculated using the MDRD equation for creatinine and the 2012 CKD-EPI equation for cystatin C. Statistical analyses included independent Student's t-test, paired t-test, Pearson's correlation, and Receiver Operating Characteristic (ROC) curve analysis.

Results: Mean HbA1c, serum creatinine, and serum cystatin C levels were significantly higher in T2DM cases than in healthy controls. Mean eGFR was significantly lower in diabetic patients compared to controls with both the MDRD equation (84.84 mL/min/1.73 m^2 vs. 98.07 mL/min/1.73 m^2) and the CKD-EPI cystatin C equation (79.2 mL/min/1.73 m^2 vs. 90.35 mL/min/1.73 m^2). A paired t-test demonstrated no statistically significant difference between eGFR calculated by MDRD and CKD-EPI ($p = 0.318$). Both eGFR estimates showed a significant inverse correlation with HbA1c ($p < 0.05$). ROC curve analysis showed excellent and comparable diagnostic performance for detecting early renal impairment (eGFR< 90 mL/min/1.73 m), with an area under the curve (AUC) of 0.95 (95% CI: 0.93–0.98) for creatinine-based eGFR and 0.96 (95% CI: 0.93–0.98) for cystatin C-based eGFR.

Conclusion: Both creatinine-based (MDRD) and cystatin C-based (CKD-EPI) eGFR equations provide comparable clinical performance in evaluating renal function in patients with type 2 diabetes mellitus. Poorer glycemic control correlates with declining GFR, highlighting the value of early eGFR assessment alongside glycemic monitoring to identify individuals at risk of diabetic kidney disease.

Keywords: Type 2 Diabetes Mellitus, Glycated Hemoglobin, Estimated Glomerular Filtration Rate, Creatinine, Cystatin C, MDRD, CKD-EPI.

Indian J. Pharm. Biol. Res. (2026): https://doi.org/10.30750/ijpbr.14.3.35

Introduction

Diabetes mellitus (DM) is a major global health problem characterized by chronic hyperglycemia and is associated with several microvascular complications, including diabetic kidney disease (DKD), one of the leading causes of chronic kidney disease (CKD) and end-stage renal disease (ESRD).[1,2] Early identification of renal dysfunction is essential to delay disease progression and improve clinical outcomes.[3,4]

Glomerular filtration rate (GFR) is considered the best overall indicator of kidney function. Since direct measurement of GFR is expensive and impractical in routine clinical practice, estimated GFR (eGFR) derived from endogenous biomarkers is widely used.[5-7] Serum creatinine is the conventional biomarker for estimating GFR using equations such as the Modification of Diet in Renal Disease (MDRD) equation. However, its concentration is influenced by factors such as age, sex, muscle mass, and dietary intake, limiting its sensitivity for detecting early renal impairment.[8]

Serum cystatin C, a low-molecular-weight cysteine protease inhibitor produced by all nucleated cells, has emerged as an alternative biomarker for estimating GFR.(9-11) It is freely filtered by the glomeruli and is less affected by muscle mass and dietary factors than serum creatinine, making it a potentially more sensitive marker of early renal dysfunction.[9-13] Nevertheless, serum cystatin C concentrations may also be influenced by non-renal factors

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How to cite this article: Moizuddin MM, Volturi J, Omer SJ. Comparison of Creatinine and Cystatin C-based Estimated Glomerular Filtration Rate in Relation to Glycemic Control Among Patients With Type 2 Diabetes Mellitus. Indian J. Pharm. Biol. Res. 2026;14(3):219-225.

Source of support: Nil

Conflict of interest: None.

Received: 28/06/2026 **Revised:** 03/07/2026 **Accepted:** 20/07/2026 **Published:** 01/08/2026

such as age, obesity, thyroid dysfunction, inflammation, and corticosteroid therapy.[14-16]

Poor glycemic control is a major determinant of diabetic nephropathy, and glycated hemoglobin (HbA1c) is a reliable indicator of long-term glycemic status. Persistent hyperglycemia accelerates renal injury through multiple pathogenic mechanisms, resulting in a progressive decline in renal function.[17-19] Therefore, assessment of renal function in relation to glycemic control may facilitate early identification of patients at increased risk of diabetic nephropathy.

Although several studies have compared creatinine- and cystatin C-based estimates of GFR, evidence from the Indian population remains limited, and the relationship between these biomarkers and glycemic control has not been adequately explored.[1,3,18,20,21] Therefore, the present study was undertaken to compare eGFR estimated using serum creatinine with the MDRD equation and serum cystatin C with the CKD-EPI equation in patients with type 2 diabetes mellitus and healthy controls. In addition, the study evaluated the association between these eGFR estimates and glycemic control to determine their utility in the early assessment of renal dysfunction.

Materials and Methods

Study Design and Participants:

This hospital-based cross-sectional case–control study was conducted in the Department of Biochemistry, Gandhi Hospital, Secunderabad, Telangana, India, from June 2021 to June 2022 after obtaining approval from the Institutional Ethics Committee. Written informed consent was obtained from all participants before enrolment.

A total of 150 participants aged 25–70 years were included in the study, comprising 75 clinically diagnosed patients with type 2 diabetes mellitus (T2DM) and 75 apparently healthy age-matched controls.

Inclusion Criteria

The case group included patients diagnosed with T2DM for more than five years attending the outpatient department. Apparently healthy individuals without a history of diabetes served as the control group.

Exclusion Criteria

Patients with hypertension, known chronic kidney disease, hepatic disorders, malignancy, muscular disorders, anaemia, haemoglobinopathies, pregnancy, recent blood transfusion, or those undergoing dialysis were excluded from the study.

Sample Collection and Laboratory Analysis

After an overnight fast, venous blood samples were collected under aseptic precautions into EDTA and plain vacutainers. Whole blood collected in EDTA tubes was used for glycated haemoglobin (HbA1c) estimation by high-performance liquid chromatography (HPLC), while serum separated from plain tubes was used for biochemical analyses. Serum creatinine was measured using the enzymatic method, and serum cystatin C was estimated by an immunoturbidimetric assay using the Beckman AU5800 automated clinical chemistry analyser.

Estimation of eGFR

Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) equation based on serum creatinine (17) and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2012 cystatin C equation based on serum cystatin C.[7,20]

MDRD equation: [8]

$175 \times (\text{serumcreatinine}) - 1.154 \times (\text{age}) - 0.203 \times 0.742$ (iffemale)$\times 1.212$(if black)

CKD-EPI (2012) Cystatin C equation:[20]

$133 \times \min(S\,cys/0.8, 1)^{-0.499} \times \max(S\,cys/0.8, 1)^{-1.328} \times 0.996^{Age} \times 0.932$[iffemale]

Statistical Analysis

Data were entered into Microsoft Excel and analysed using SPSS version 20.0. Continuous variables were expressed

as mean ± standard deviation (SD). Comparisons between groups were performed using the independent Student's *t*-test. Pearson's correlation coefficient was used to assess the relationship between eGFR and biochemical variables. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of creatinine- and cystatin C-based eGFR in identifying renal impairment. A *p*-value <0.05 was considered statistically significant.

Results

A total of 150 participants were included, comprising 75 patients with T2DM and 75 healthy controls. There was no statistically significant difference in age between the two groups (62 ± 6 vs. 60 ± 7 years, p = 0.06), indicating comparable baseline characteristics (Table 1).

The mean HbA1c, serum creatinine, and serum cystatin C levels were significantly higher in patients with T2DM than in healthy controls. Conversely, the mean estimated glomerular filtration rate (eGFR) was significantly lower in cases than in controls, irrespective of the equation used for estimation. The mean eGFR calculated using the MDRD equation was 84.84 mL/min in cases and 98.07 mL/min in controls, whereas the mean eGFR estimated using the CKD-EPI cystatin C equation was 79.21 mL/min and 90.35 mL/min, respectively (Table 1).

Pearson's correlation analysis demonstrated a significant negative correlation between serum creatinine and creatinine-based eGFR (MDRD) ($p< 0.001$). Similarly, serum cystatin C showed a significant inverse correlation with cystatin C-based eGFR (CKD-EPI) ($p< 0.001$) (Figures 1 and 2).

Comparison of eGFR values obtained using the MDRD and CKD-EPI cystatin C equations by paired *t*-test showed no statistically significant difference between the two methods ($p = 0.318$) (Table 2).

Glycemic status, assessed by HbA1c, demonstrated a significant negative correlation with eGFR estimated using both creatinine- and cystatin C-based equations, indicating that poorer glycemic control was associated with lower renal function ($p< 0.05$) (Table 3).

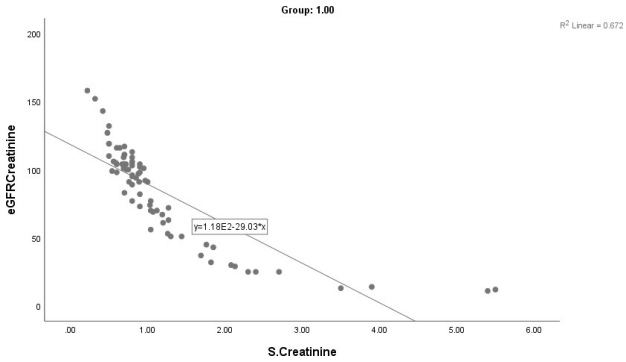

Figure 1: Scatter plot illustrating the negative linear correlation between serum creatinine and creatinine-based estimated glomerular filtration rate (MDRD equation) among study participants (r = -0.27, p = 0.020).

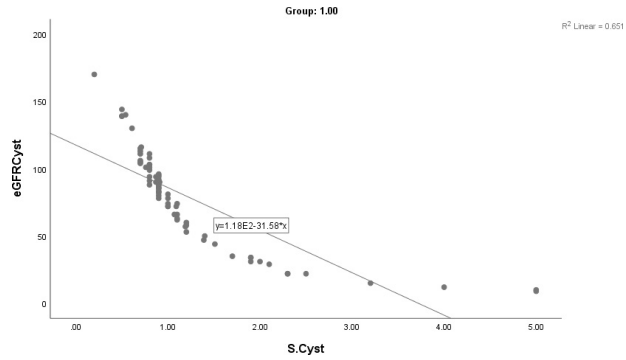

Figure 2: Scatter plot illustrating the negative linear correlation between serum cystatin C and cystatin C-based estimated glomerular filtration rate (CKD-EPI equation) among study participants (r = -0.25, p = 0.030)

Receiver operating characteristic (ROC) curve analysis was performed to evaluate the ability of both eGFR equations to identify individuals at risk of renal impairment using an eGFR cut-off of <90 mL/min/1.73 m²,

Table 1: Demographic and Biochemical Characteristics of the Study Population

Variable	*Cases (n = 75) Mean ± SD*	*Controls (n = 75) Mean ± SD*	*p value*
Age (years)	62 ± 6	60 ± 7	0.06
HbA1c (%)	7.69 ± 0.70	4.54 ± 0.40	<0.001
Serum Creatinine (mg/dL)	1.15 ± 0.10	0.81 ± 0.08	<0.001
Serum Cystatin C (mg/L)	1.21 ± 0.10	1.00 ± 0.10	<0.001
eGFR (MDRD) (mL/min/1.73 m²)	84.84 ± 8.30	98.07 ± 9.70	<0.001
eGFR (CKD-EPI) (mL/min/1.73 m²)	79.21 ± 8.00	90.35 ± 8.80	<0.001

Table 2: Comparison of eGFR Calculated Using MDRD and CKD-EPI Cystatin C Equations in T2DM Cases

Comparison	*Mean ± SD*	*Mean difference*	*p-value*
eGFR (MDRD)	84.84 ± 8.3	5.63	0.318
eGFR (CKD-EPI)	79.21 ± 8.0		

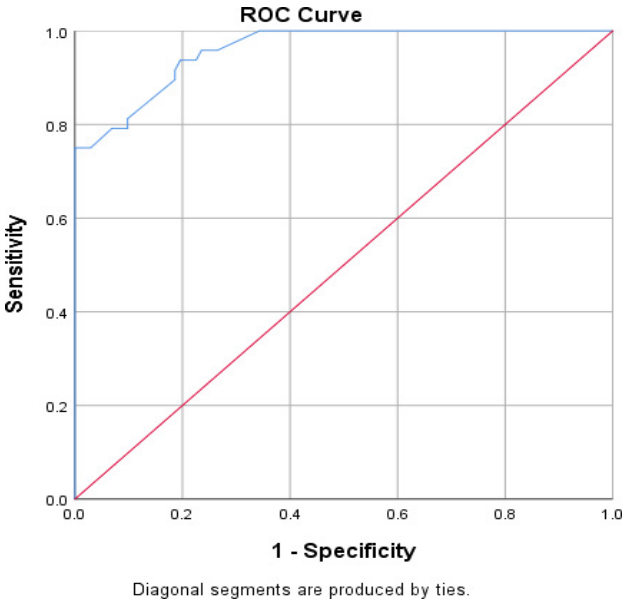

Figure 3: Receiver Operating Characteristic (ROC) curve of creatinine-based eGFR (MDRD equation) for predicting early renal impairment (eGFR< 90 mL/min/1.73 m).

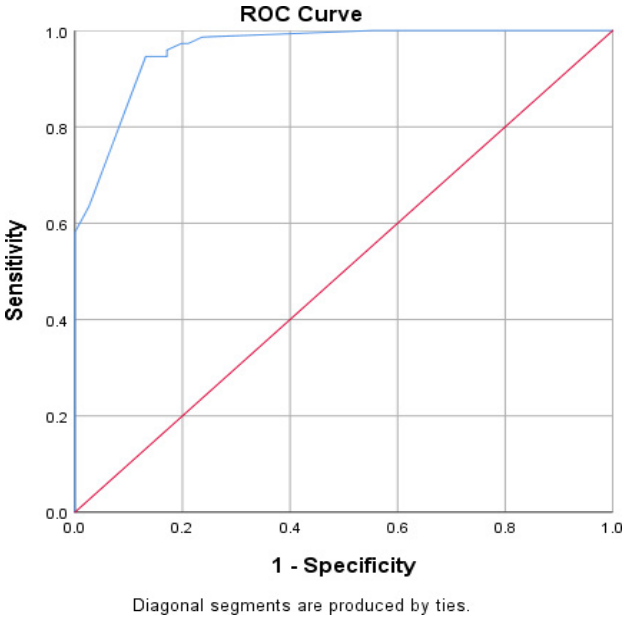

Figure 4: Receiver Operating Characteristic (ROC) curve of cystatin C-based eGFR (CKD-EPI equation) for predicting early renal impairment (eGFR < 90 mL/min/1.73 m).

Table 3: Pearson Correlation Analysis Between Glycemic Status (HbA1c) and eGFR Estimates

Pearson	*Correlation*	*p-value*
HbA1c vseGFR (MDRD)	-0.27	0.02
HbA1cvseGFR (CKD-EPI)	-0.25	0.03

Table 4: Receiver Operating Characteristic (ROC) Analysis for Diagnostic Accuracy in Identifying Renal Dysfunction (eGFR< 90 mL/min/1.73 m)

Parameter	*AUC (95% CI)*	*p-value*
eGFR (MDRD)	0.95 (0.93–0.98)	<0.001
eGFR (CKD-EPI)	0.96 (0.93–0.98)	<0.001

corresponding to mildly decreased kidney function according to the National Kidney Foundation/KDIGO classification.(6,22) The area under the curve (AUC) was 0.95 (95% CI: 0.93–0.98) for creatinine-based eGFR and 0.96 (95% CI: 0.93–0.98) for cystatin C-based eGFR, indicating excellent and comparable diagnostic performance of both equations (Figure 3, Figure 4, Table 4).

Discussion

The present study compared serum creatinine- and cystatin C-based estimated glomerular filtration rate (eGFR) in patients with type 2 diabetes mellitus (T2DM) and evaluated their association with glycemic control. The principal findings were: (i) patients with T2DM had significantly higher HbA1c, serum creatinine, and serum cystatin C levels than healthy controls; (ii) eGFR estimated using both the MDRD and CKD-EPI cystatin C equations was significantly lower in diabetic patients; (iii) eGFR showed a significant inverse correlation with serum creatinine, serum cystatin C, and HbA1c; and (iv) both equations demonstrated comparable performance in estimating renal function.

Diabetic kidney disease is one of the most common microvascular complications of T2DM and remains a leading cause of chronic kidney disease and end-stage renal disease worldwide. Persistent hyperglycemia induces oxidative stress, advanced glycation end-product formation, glomerular hyperfiltration, and inflammatory changes that progressively impair renal function. Consequently,

early assessment of kidney function is essential for timely intervention and prevention of disease progression. [2, 4, 6]

In the present study, patients with T2DM had significantly higher HbA1c levels than controls, indicating suboptimal glycemic control. Poor glycemic control is a well-established risk factor for the development and progression of diabetic nephropathy. Chronic hyperglycemia promotes structural and functional alterations in the glomerulus, leading to a gradual decline in glomerular filtration rate.[12,17] The significant negative correlation observed between HbA1c and eGFR in the present study supports this relationship and emphasizes the importance of maintaining adequate glycemic control to preserve renal function.

Serum creatinine remains the most widely used endogenous biomarker for estimating GFR because of its availability and low cost. However, serum creatinine is influenced by age, sex, muscle mass, and dietary intake, which may limit its sensitivity for detecting early renal impairment.[8] In the present study, serum creatinine levels were significantly higher in patients with T2DM, and an inverse correlation was observed between serum creatinine and creatinine-based eGFR, consistent with the expected physiological relationship.

Serum cystatin C has gained increasing attention as an alternative biomarker of renal function because it is produced at a relatively constant rate by nucleated cells and is less affected by muscle mass and dietary factors.[9-11] In the present study, serum cystatin C concentrations were significantly higher among diabetic patients, with a corresponding reduction in cystatin C-based eGFR. These findings are consistent with previous reports demonstrating that cystatin C is a sensitive marker of declining renal function in patients with diabetes.[13,20]

Comparison of eGFR estimated using the MDRD and CKD-EPI equations did not demonstrate a statistically significant difference in this study population. Furthermore, ROC curve analysis demonstrated comparable diagnostic performance for both equations in identifying participants at risk of renal impairment. These findings suggest that, within the study population, both creatinine and cystatin C-based equations provided similar estimates of renal function. Previous studies have reported conflicting findings regarding the superiority of cystatin C over creatinine. While Mussap *et al*. and Macisaac *et al*. observed greater sensitivity of cystatin C-based equations for detecting early renal impairment,[13,21] Oddoze *et al*. reported that serum creatinine performed comparably in diabetic patients.[23] Similarly, Harmoinen *et al*. demonstrated good diagnostic performance of cystatin C in estimating GFR among patients with T2DM.[24] Our findings support the use of either biomarker for estimating renal function in routine clinical practice, particularly in patients with preserved or mildly impaired kidney function.

The inverse association between HbA1c and eGFR observed in the present study further highlights the close relationship between long-term glycemic control and renal function. Similar observations have been reported by Sim *et al*., who demonstrated an association between elevated HbA1c and serum cystatin C levels,[18] and by Oezkur *et al*., who reported that chronic hyperglycemia increases the risk of renal injury.[19] These findings reinforce the importance of routine monitoring of both glycemic status and renal function in patients with T2DM to facilitate early detection of diabetic kidney disease.

The present study has several strengths. Both serum creatinine and serum cystatin C were evaluated simultaneously in the same study population using standardized laboratory methods, allowing direct comparison of two commonly used eGFR equations. In addition, the relationship between renal function and glycemic control was evaluated, providing clinically relevant information for the assessment of diabetic nephropathy.

However, certain limitations should be acknowledged. The study was conducted at a single center with a relatively small sample size and a cross-sectional design, limiting the generalizability of the findings and precluding causal inference. Measured GFR using a reference method was not available for validating the estimated equations. Furthermore, urinary albumin excretion, an important marker of early diabetic kidney disease, was not assessed. Factors known to influence serum cystatin C concentrations, including obesity, thyroid dysfunction, corticosteroid use, and inflammatory status, were also not evaluated. [14-16]

Overall, the findings of the present study indicate that both creatinine- and cystatin C-based eGFR equations provide comparable estimates of renal function in patients with T2DM. Larger prospective studies incorporating measured GFR and urinary albumin assessment are warranted to further establish their comparative diagnostic performance for the early detection of diabetic kidney disease.

Conclusion

The present study demonstrated that patients with type 2 diabetes mellitus had significantly reduced eGFR and higher serum creatinine and cystatin C levels compared with healthy individuals. Estimated GFR derived from

both the MDRD (creatinine-based) and CKD-EPI (cystatin C-based) equations showed a significant inverse association with HbA1c, highlighting the relationship between poor glycemic control and declining renal function. Both equations demonstrated comparable performance in estimating renal function in the study population.

These findings suggest that either creatinine- or cystatin C-based eGFR may be used for routine assessment of renal function in patients with type 2 diabetes mellitus. Early estimation of eGFR, together with optimal glycemic control, may facilitate timely identification of patients at risk of diabetic kidney disease and enable appropriate interventions to delay disease progression. Further large-scale prospective studies incorporating measured GFR and urinary albumin assessment are warranted to validate these findings and establish the comparative clinical utility of both biomarkers.

Acknowledgement

Authors would like to express their gratitude to the hospital staff and patients for supporting us in collecting the information smoothly.

Conflict of Interest

The authors declare that there is no conflict of interest.

Ethics Committee Approval

The study was approved by the Institutional Ethics committee dated

Financial Disclosure

The authors declared that this study has received no financial support.

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