Comparative Evaluation of Cystatin C and Conventional Renal Markers for Early Detection of Renal Dysfunction in Type 2 Diabetes Mellitus (T2DM).

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Abstract:

Background:

Early detection of renal functional changes in type 2 diabetes mellitus (T2DM) is essential to prevent progression to chronic kidney disease. Conventional renal biomarkers such as serum creatinine and urea often fail to detect early impairment because they typically rise only after substantial loss of renal function. This study evaluated whether serum cystatin C provides greater sensitivity for identifying early renal functional changes in T2DM.

Methods:

A comparative cross-sectional study was conducted involving 30 patients with T2DM and 30 healthy controls aged 30-70 years with comparable sex distribution. Serum levels of random blood

sugar (RBS), glycated haemoglobin (HbA1c), urea, creatinine, and cystatin C were measured. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Statistical analyses were performed using SPSS version 25.

Results:

The T2DM group showed significantly higher levels of RBS (220.10 ± 92.9 mg/dL), HbA1c (8.68 ± 1.7%), urea (24.23 ± 13.4 mg/dL), and cystatin C (1.25 ± 0.6 mg/L) compared with controls ($p = 0.001$ for RBS, HbA1c, and cystatin C; $p = 0.01$ for urea). Serum creatinine and eGFR did not differ significantly between groups. Receiver operating characteristic analysis demonstrated superior discrimination for cystatin C (AUC = 0.78) compared with urea (AUC = 0.63) and creatinine (AUC = 0.55).

Conclusion:

Serum cystatin C demonstrated greater sensitivity than conventional renal markers for detecting early renal functional changes in T2DM and may complement routine renal assessment.

Keywords: Cystatin C, Diabetes Mellitus, Renal Impairment, Biomarker, Kidney Dysfunction.

1. Introduction :

Type 2 diabetes mellitus (T2DM) is one of the most common chronic metabolic disorders worldwide, characterized by insulin resistance, impaired insulin secretion, and sustained hyperglycemia. During the last decades, T2DM has demonstrated an astonishing increase in its incidence globally due to lifestyle changes, sedentary activities, and obesity. According to the IDF Diabetes Atlas of 2021, approximately 537 million adults worldwide currently have diabetes, a number predicted to increase significantly by 2045, reaching approximately 780 million [1]. Among the complications of diabetes, diabetic kidney disease remains a leading cause of Chronic Kidney Disease (CKD) and End-Stage Renal Disease (ESRD) worldwide [2].

The kidneys are important for maintaining physiological balance through filtration, reabsorption, and excretion. Over time, chronic hyperglycemia leads to metabolic and hemodynamic alterations that cause progressive injury to renal structures. Early signs include increased glomerular filtration, basement

membrane thickening, and mesangial expansion, which may progress to glomerulosclerosis and nephron loss [3, 4]. Microalbuminuria is widely regarded as an early clinical indicator of diabetic kidney involvement; however, functional renal changes may precede detectable urinary abnormalities, highlighting the need for sensitive serum biomarkers [5].

Traditionally, renal function is assessed by measuring serum urea and creatinine and estimating the glomerular filtration rate (GFR). However, although these methods have been widely used clinically, they still have notable limitations. The most commonly used biomarker, serum creatinine, is influenced by factors such as muscle mass, age, sex, dietary habits, and hydration status, and typically does not increase until nearly half of renal function has been compromised [6]. Also, serum urea levels are affected not only by kidney function but also by a range of non-renal factors, including dietary protein intake, liver health, and metabolic states involving increased catabolism. Because of these influences, its diagnostic specificity is somewhat limited. While eGFR formula estimates tend to improve diagnostic accuracy, they still heavily depend on serum creatinine and may fail to detect early renal dysfunction in diabetic and elderly individuals [7, 8].

In contrast, cystatin C levels are more consistent across populations and less confounded by these factors, thereby offering superior reliability for detecting early renal dysfunction [9, 10]. This biomarker is superior in several studies and meta-analyses for early detection of CKD and for predicting cardiovascular and all-cause mortality in diabetic patients [11, 12].

Early detection of renal functional alterations in patients with diabetes allows timely implementation of renoprotective strategies, including optimized glycemic and blood pressure control, and the use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) to prevent or delay the onset of ESRD and its cardiovascular complications [13, 14]. The use of cystatin C, which responds more rapidly to changes in GFR than creatinine, can provide clinicians with a faster and more accurate tool for assessing renal function. Such advances offer promising improvements in patient outcomes in the management of diabetic nephropathy [9, 15].

Despite its recognized advantages, data on the application of cystatin C within local diabetic populations, especially in developing healthcare systems where CKD is often underdiagnosed, remain limited. The evaluation of cystatin C along with traditional renal markers could enhance early detection

and improve clinical decision-making in resource-poor settings. Therefore, this study aims to assess the diagnostic performance of serum cystatin C as an early marker of renal dysfunction in T2DM patients and compare its diagnostic utility with that of traditional renal function markers, such as serum creatinine, urea, and eGFR. This study reports the sensitivity and specificity of cystatin C, providing evidence to support recommending its inclusion in routine follow-up for diabetic patients.

2. Methodology

2.1 Study Design and Population

This study was a comparative cross-sectional study involving two groups: a diabetic group of T2DM patients diagnosed who do not exercise regularly, and a normal/sedentary control group of 30 healthy individuals who do not engage in any regular physical activity. Diabetic patients were selected based on a clinical diagnosis of T2DM, as approved by the patient's physician. The control subjects were healthy, non-diabetic individuals with normal random blood glucose levels and no metabolic complications. The two groups were selected to achieve a comparable sex distribution; however, age differed between groups and was therefore included as a covariate in adjusted analyses. Participants were recruited from a nearby hospital, and the study was approved by the institutional ethics review board.

2.2 Inclusion Criteria

For this study, the samples and data that were analysed were collected from the Al-Karama hospital, and the analysed data were divided into two groups:

- Diabetic group: Patients with T2DM, aged 30-70 years.
- Control group: the healthy group's ages range from 30 to 70 years.

2.3 Exclusion Criteria

- Participants with any history of chronic kidney disease, liver disease, or other major systemic illnesses.
- The Age Group of pregnant women and young people aged 30 years or less.

2.4 Biochemical Analysis:

The following biochemical markers were measured for both the diabetes and healthy groups.

1. Random Blood Sugar (RBS): venous blood samples were obtained from each subject. RBS was tested on the standard enzymatic colorimetric method (LINEAR CHEMICS). The values were given in terms of mg/dL.
2. Glycated Haemoglobin (HbA1c): Serum HbA1c was measured by HPLC and analysed according to previously developed laboratory protocols [16]. The outcomes were expressed as percentages for reporting purposes [17].
3. Urea: Serum urea levels were estimated by the enzymatic colorimetric method of the reagents from Linear Chemicals. Urea concentration was reported in milligrams per decilitre.
4. Creatinine: S.K. creatinine levels were determined by the Kinetic colorimetric method, and the reagents used were from (LINEAR CHEMICALS). The results were reported as mg/dL.
5. Cystatin C: Cystatin C protein concentration was quantified using a specific human cystatin C ELISA kit (lab119589). The results were calculated based on mg/L.

2.5 Demographic and Clinical Information:

The Age of each participant was documented at enrolment. The gender composition in both groups was documented.

2.6 Statistical Analysis

Data were evaluated utilizing SPSS version 25 (IBM, USA). Descriptive statistics, encompassing mean and standard deviation (SD Mean), were computed for all variables. The disparities between diabetes and control cohorts were assessed utilizing independent t-tests for continuous variables (RBS, HbA1c, Urea, Creatinine, Cystatin C, and Age). Multivariable linear regression analyses were performed for renal biomarkers with adjustment for age and sex. A p-value below 0.05 was deemed statistically significant for evaluating gender distribution between the two groups; the chi-square test was used.

3. Results

The results of the study comparing various biochemical markers were analysed in 30 diabetic patients compared to the control group as follows:

3.1 Random Blood Sugar (RBS)

Individuals diagnosed with diabetes showed significantly higher RBS levels compared to the control group (see Table 1). The differences between the two groups were statistically significant, reinforcing the importance of RBS as a key indicator for diabetes.

Table 1: Comparison of Random Blood Sugar (RBS) Levels between Diabetic Patients and Control Subjects

Group	RBS (mg/dL) ± (SD)	*p*-value
Diabetic Patients	220.10 ± 92.9	0.001
Control Subjects	93.07 ± 11.9	

3.2 Glycated Haemoglobin (HbA1c)

The HbA1c levels were markedly higher in the diabetes group than in the control group (Table 2). A *p*-value of <0.001 signifies a highly significant disparity between the groups, corroborating inadequate glycemic control in the diabetes cohort.

Table 2: Comparison of Glycated Haemoglobin (HbA1c) Levels between Diabetic Patients and Control Subjects

Group	HbA1c ± (SD)	*p*-value
Diabetic Patients	8.68 ± 1.7	0.001
Control Subjects	5.02 ± 0.4	

3.3 Urea

As shown in Table 3, urea levels were significantly higher in the diabetic group than in control subjects. The *p*-value of 0.01 suggests that diabetes may be associated with renal stress or dysfunction, as urea is a marker for kidney function.

Table 3: Comparison of Urea Levels between Diabetic Patients and Control Subjects

Group	Urea (mg/dL) ± (SD)	*p*-value
Diabetic Patients	24.23 ± 13.4	0.01
Control Subjects	16.10 ± 5.6	

3.4 Creatinine

There was no significant difference in serum creatinine levels between the diabetic groups (Table 4). This indicates that creatinine may not be a sensitive marker for detecting renal dysfunction in the early stages of diabetes.

Table 4: Comparison of Creatinine Levels between Diabetic Patients and Control Subjects

Group	Creatinine (mg/dL) ± (SD)	*p*-value
Diabetic Patients	0.822 ± 0.2	0.086
Control Subjects	0.731 ± 0.1	

3.5 Cystatin C

Serum cystatin C levels were significantly higher in the diabetes group than in the control group. Serum cystatin C levels increase as an indicator of glomerular filtration rate and serve as a more sensitive marker of early reduced kidney function in patients with diabetes (Table 5).

Table 5: Comparison of Cystatin C Levels between Diabetic Patients and Control Subjects

Group	Cystatin C (mg/L) ± (SD)	*p*-value
Diabetic Patients	1.25 ± 0.6	0.001
Control Subjects	0.65 ± 0.1	

After adjustment for age and sex, serum cystatin C remained significantly higher in diabetic patients compared with controls (adjusted $p < 0.05$), whereas creatinine remained non-significant.

3.6 Age

The mean age of diabetic patients (46.77 ± 16.2 years) was significantly higher than that of control subjects (38.30 ± 12.5 years), as shown in Table 6 ($p = 0.046$). This statistically significant age difference suggests that age may have contributed to the observed differences in biochemical markers

between the two groups. Therefore, age should be considered a potential confounding factor when interpreting the study's findings.

Table 6: Comparison of Mean Age between Diabetic Patients and Control Subjects:

Group	Age (years) ± (SD)	*p*-value
Diabetic Patients	46.77 ± 16.2	0.046
Control Subjects	38.30 ± 12.5	

3.7 eGFR

There was no significant difference in GFR between the diabetic and control groups. This indicates that GFR may not be a sensitive marker for detecting renal dysfunction in the early stages of diabetes (Table 7).

Table 7: Comparison of GFR Mean Between Diabetic Patients and Control Subjects

Group	eGFR ± (SD)	*p*-value
Diabetic Patients	107.73 ± 12.3	0.21
Control Subjects	111.57 ± 15.3	

3.8 Gender

There were no differences between males and females in either group (p=1.000), and biochemical markers in this study showed that gender had no effect.

Table 8: Gender Distribution in Diabetic and Control Groups

Group	Male (%)	Female (%)	*p*-value
Diabetic Patients	47.2	52.8	1.000
Control Subjects	46.7	53.3	

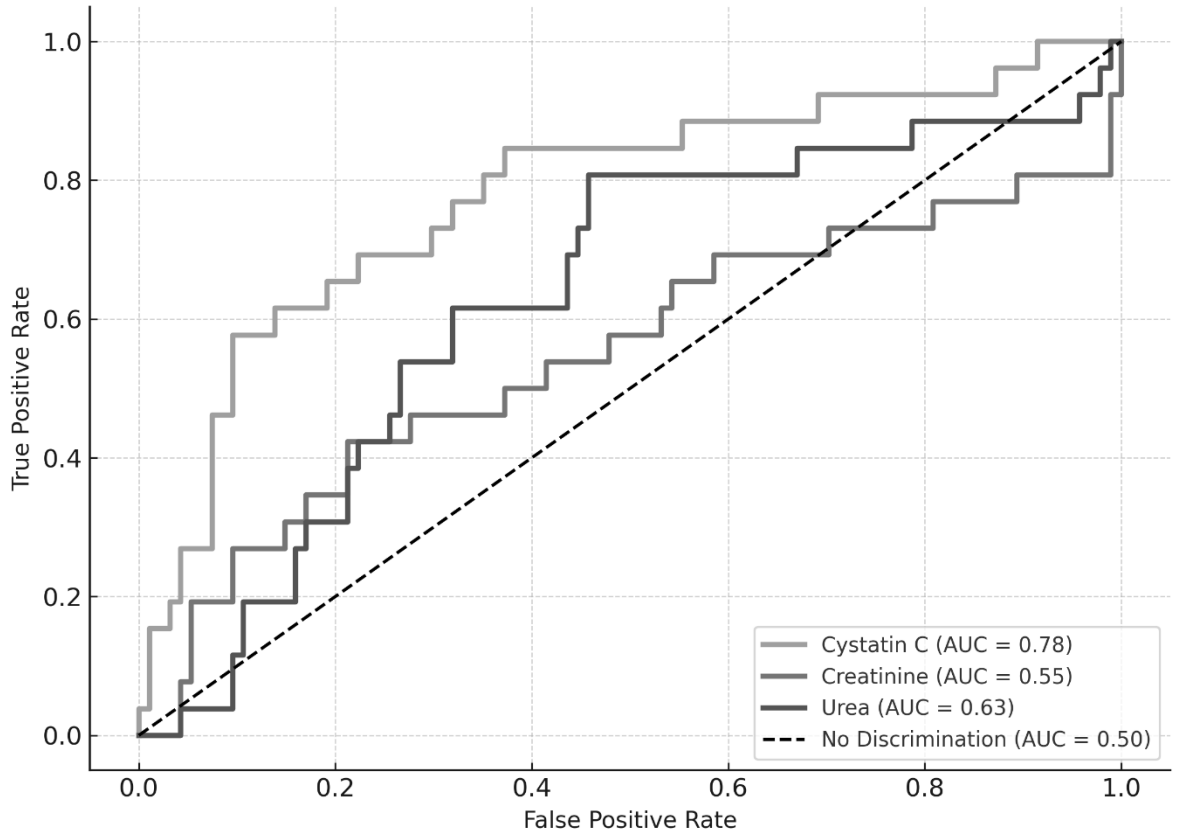

Figure 1. Receiver Operating Characteristic (ROC) curves comparing the diagnostic performance of serum Cystatin C, creatinine, and urea in detecting early renal dysfunction

To evaluate the diagnostic accuracy of Cystatin C compared to traditional renal biomarkers, ROC curves were plotted using an eGFR threshold of <90 mL/min/1.73 m². A subset of participants met the criterion for early renal functional decline, which served as the reference standard for ROC analysis. As shown in Figure 1, Cystatin C exhibited the highest AUC (0.78), followed by urea (0.63) and creatinine (0.55). This reinforces our finding that Cystatin C detects early renal changes more effectively than conventional markers in T2DM patients.

4. Discussion:

Our findings reinforce the well-known roles of Random Blood Sugar (RBS) and glycated haemoglobin (HbA1c) in evaluating diabetes. They also point to serum cystatin C as a more sensitive marker of early kidney involvement in T2DM. The RBS levels were elevated in the group with diabetes,

indicating ongoing hyperglycemia and consistent with the diagnostic standards set by the American Diabetes Association [18]. Previous studies also reported similar elevations in RBS among individuals with diabetes, supporting its value as an initial screening tool [19-21].

HbA1c levels were notably elevated in the diabetic group compared with the control group, reflecting diminished long-term glycemic control (Table 2). The association between chronic hyperglycemia and diabetes-related complications is well recognized, mainly driven by mechanisms involving oxidative stress and vascular injury [22]. Our results align with previous research indicating that HbA1c remains a reliable indicator of long-term glucose control and treatment adherence [23].

Serum urea was also elevated in the diabetic participants (Table 3), which aligns with evidence that metabolic changes in diabetes can place early stress on the glomeruli [24, 14, 25]. These findings align with the suggestions of Kulkarni et al., who emphasized the importance of early biochemical monitoring to delay the onset of nephropathy [26]. In contrast, creatinine levels did not differ significantly between groups (Table 4), which is expected because creatinine generally rises only after substantial nephron loss [15, 27]. This highlights the limitation of creatinine in detecting early kidney dysfunction.

The ROC curve analysis further highlights the value of cystatin C in identifying early renal functional changes in patients with T2DM. With an AUC of 0.78, it demonstrated a notably higher predictive accuracy than both creatinine and urea, which yielded AUCs of 0.55 and 0.63, respectively (Figure 1). Cystatin C, however, showed a clear elevation in individuals with diabetes (Table 5), indicating reduced filtration efficiency before any changes in creatinine become apparent. Earlier work has reached similar conclusions, demonstrating that cystatin C identifies mild declines in GFR more reliably than traditional renal markers in patients with diabetes [28, 12]. Taken as a whole, the data highlight cystatin C as a helpful marker for detecting renal impairment at an early stage.

The age differences observed between the study groups (Table 6) are consistent with established epidemiological trends, as both diabetes and susceptibility to renal impairment increase with advancing age [29, 4, 30]. Although age may account for some biochemical variability, the marked elevation of cystatin C in the diabetic group suggests an early renal effect that cannot be explained solely by aging.

These results support the role of cystatin C as a sensitive biomarker for early renal functional changes in patients with T2DM. Including cystatin C in routine clinical assessments may allow earlier recognition of kidney involvement and help prevent progression to chronic kidney disease or ESRD.

This study focused on functional renal biomarkers and did not include urinary markers of kidney damage; therefore, conclusions are limited to early renal functional changes rather than formal staging of diabetic kidney disease.

5. Conclusion:

Serum cystatin C levels were noticeably higher in people with T2DM than in the control group, even though their creatinine and eGFR values were still within normal limits. This pattern suggests that cystatin C can reveal early signs of kidney dysfunction before more obvious clinical changes appear. Routinely assessing serum cystatin C in patients with T2DM may facilitate earlier recognition of subclinical renal functional changes and complement conventional renal biomarkers. Further large-scale and longitudinal studies are required to establish clinical cut-off values and prognostic implications.

Future large-scale, longitudinal, and multicentre studies are recommended to validate these findings and establish standardized cystatin C cut-off values for early-stage diabetic kidney disease detection across diverse populations.

CONFLICT OF INTEREST (COI).
The authors declare that there are no competing interests.

DECLARATION OF GENERATIVE AI IN MANUSCRIPT PREPARATION.
Grammarly software (version 14.1253.1) was used to support language editing and improve the readability of the manuscript. The authors have thoroughly reviewed and edited the manuscript and assume full responsibility for its accuracy and publication.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE
The study received approval from the Ethical Review Committee at Ibn Sina University of Medical and Pharmaceutical Sciences (Reference: ISU.20.1.25).

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