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Original Research Article

Serum Cystatin C: An Innovative Biomarker for Early Renal Impairment in Diabetes

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Abstract

Background: Diabetic nephropathy has been identified as one of the primary contributors to chronic kidney disease (CKD) in the world today. Conventional indicators of early renal impairment such as serum creatinine and microalbuminuria, are often missed. Serum cystatin C (CysC) is perhaps one of indicators of an early glomerular dysfunction.

Objective: To assess the diagnostic value of serum cystatin C for detection of early renal impairment in individuals with type 2 diabetes mellitus (T2DM).

Methods: This cross-sectional analytical study entailed 150 participants; 75 of them were healthy controls (HCs), whereas 75 suffered type 2 diabetes. Renal functioning was determined by serum creatinine (SCr), urine albumin creatinine ratio (UACR), assessed glomerular filtration rate (eGFR), CysC. Statistical comparisons and correlation analysis were made.

Results: The CysC levels of T2DM patient have been found to be significantly higher compared to controls ($p < 0.001$). Even with normal serum creatinine, normoalbuminuric diabetic patients still had high cystatin C levels ($p < 0.01$). The relationship of cystatin C with eGFR was more negative than that of creatinine ($r=-0.72$ and $r=-0.58$, respectively).

Conclusion: CysC is accurate and sensitive biomarker of early renal deterioration in diabetic individuals that could help with earlier management before nephropathy would become evident.

Keywords: Cystatin C; Early Renal Impairment; Diabetic Nephropathy; Diabetes Mellitus; Renal Dysfunction.

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Introduction

"Diabetes mellitus (DM)" is major primary cause of "end-stage renal disease (ESRD)" and "CKD", and public health issue globally. T2DM is on the increase worldwide coinciding with the incidence of diabetic nephropathy (DN). [1] Early diagnosis and treatment are essential to prevent permanent damage to the kidneys because out of 30-40 percent of diabetic patients, problems with kidneys arise eventually. [2] The hallmarks of DN have been mesangial expansion, progressive glomerular damage, basement membrane thickening along with eventual reduction in "glomerular filtration rate (GFR)". Conventional ways of screening diabetic kidney disease include estimation of GFR, serum creatinine measurement, microalbuminuria. [3] However, the sensitivity of serum creatinine in identifying early renal failure is limited due to its dependence on dietary consumption, age, sex, and muscle mass. [4] Crucially, until around 50% of renal function is lost, serum creatinine levels might stay in normal reference range. [5] It has long been believed that microalbuminuria is an early sign of DN. However, new data indicates that renal alterations, both structural and functional, might take place before observable rises in the excretion of albumin in the urine. [6] Furthermore, microalbuminuria may regress as blood pressure and glucose levels increase, making it less reliable as a stand-alone indicator of early nephropathy. [7]

More sensitive and specific biomarkers that can detect minor declines in GFR before overt renal injury occurs are therefore desperately needed. A

low molecular weight (13 kDa) inhibitor of cysteine protease, cystatin C, has drawn interest as potential endogenous GFR monitor. It is freely filtered by glomeruli, generated at steady rate by all nucleated cells, nearly entirely reabsorbed and digested in proximal tubules without tubular secretion. [8] Cystatin C levels are a potentially improved indicator of renal function than creatinine because they are less affected by age, gender, or muscle mass.[9]

Serum cystatin C (CysC) may identify slight declines in GFR earlier than creatinine-based measures, according to a number of studies. [10] Even patients with normal blood creatinine and normo-albuminuria have been found to have higher cystatin C levels in diabetic populations, indicating early subclinical renal impairment. [11] Additionally, compared to serum creatinine, cystatin C has been demonstrated that a stronger correlation with observed GFR.[12] Cystatin C is a renal marker, but it has also been linked to systemic inflammation and cardiovascular risk, both of which are very common in diabetic individuals.[13] Its potential clinical utility in risk categorization is further highlighted by this bidirectional connection. Cystatin C is yet to be practically used in routine diabetic screening particularly in emerging medical facilities although the evidence is gradually accumulating. The methods of establishing the diagnostic value of it among diabetic patients with early renal impairment can significantly improve the outcomes and the methods of early diagnosis.

The level of CysC in T2DM patients will be measured and its diagnostic power will be compared to the more conventional renal parameters like serum creatinine and urine albumin excretion. With normo-albuminuria and normal creatinine results in patients of having diabetes, we hypothesize that CysC is a less invasive biomarker of an early renal impairment.

Materials and Methods

Over the course of a year, this cross-sectional analytical investigation was carried out in the general medicine and biochemistry departments of the ESIC Medical College and Hospital, Indore, Madhya Pradesh, India. The study aimed to estimate efficacy of blood cystatin C as an early marker of renal impairment in persons with T2DM. The Institutional Ethics Committee approved ethical clearance prior to the commencement of the investigation. All participants obtained signed informed consent in accordance with Declaration of Helsinki.

Study Population: 150 people in all, ages 35 to 65, were registered and split into two groups. 75 patients who had had a T2DM diagnosis for at least five years made up Group I. The "American Diabetes Association's criteria" have been utilized to establish diagnosis of diabetes. 75 age- and sex-matched, seemingly healthy people without diabetes or known renal illness made up Group II, which acted as controls. To reduce confounding factors influencing renal biomarkers, participants with acute kidney injury, non-diabetic hypertension, overt cardiovascular disease, thyroid disorders, pregnancy, active infections, inflammatory conditions, CKD stage 3 or higher, those taking nephrotoxic medications were excluded.

Data Collection: All the subjects were subjected to an extensive clinical history and physical examination. The demographic and clinical data (blood pressure, body mass index (BMI), sex, age, length of diabetes, medication history) were recorded using a standardized proforma. Anthropometric measurements were collected through methods that were standardised. Ten minutes of rest followed on which blood pressure was recorded in a seated position with a calibrated sphygmomanometer.

Sample Collection: About 5mL of venous blood was collected under aseptic conditions after an 8-10 hour overnight fast. The separation of serum from blood in the samples involved centrifugation of samples (10 minutes at 3000 rpm) following the coagulation of the samples. The samples were either tested immediately or stored at -20^{o}C until they were to be tested again.

Biochemical Analysis: "Fasting plasma glucose (FPG)" was assessed utilising glucose oxidase-peroxidase enzymatic technique. "Glycated hemoglobin (HbA1c)" was measured using automatic analyzer Cobas Integra400 plus. The serum creatinine levels were assessed using the IDMS-calibrated kinetic Jaffe technique. The eGFR was computed utilizing the CKD-EPI creatinine equation. Cystatin C was quantified with an automated chemistry analyzer, incorporating suitable internal quality control protocols based on a particle-enhanced immunoturbidimetric assay. A spot urine sample was utilized to assess urinary albumin and creatinine concentrations, and the UACR ratio was computed. A UACR under 30 mg/g is classified as normo-albuminuria, while a UACR between 30 and 300 mg/g is classified as microalbuminuria.

Early renal impairment was considered to be microalbuminuria and/or eGFR ranging 60-90 mL/min/1.73m^2.

Statistical Analysis: It was done using SPSS version 25. Continuous variables were presented as the mean and standard deviation. For independent samples t-test was employed to compare the groups. Pearson correlation analysis was utilized to ascertain the association among creatinine, eGFR, and

cystatin C. P-values less than 0.05 was considered statistically significant.

Results

Total 150 participants involving 75 T2DM patients and 75 HCs were involved in study. As indicated in Table 1, no significant difference was found in mean age between diabetic patients (53.8±6.4 yrs) and controls (52.9±5.8 yrs; p=0.34). However, BMI was significantly higher among diabetics (27.2±3.1kg/m²) comparing with controls (24.5±2.7kg/m²; p<0.01). Glycemic parameters were markedly elevated in diabetes group, with significantly higher FPG (158±30mg/dL v/s 91±10mg/dL; p<0.001), HbA1c levels (8.1±1.0% v/s 5.2±0.3%; p<0.001), as detailed in Table 1.

The parameters of renal functions were significantly different in 2 groups (Table 2). Diabetic patients had slightly higher serum creatinine levels compared to controls (1.01 ± 0.20 mg/dL v/s 0.88±0.14mg/dL; p=0.03). In contrast, eGFR has been significantly lesser in diabetic group (83.6±13.8mL/min/1.73m²) than in controls (99.2±11.9mL/min/1.73m²; p<0.001). UACR was also substantially elevated in diabetics (39.8±17.5mg/g) comparing with controls (11.8±4.9mg/g; p<0.001). Also, CysC was much greater in diabetic patients (1.32 ± 0.30 mg/L) compared to controls (0.81 ± 0.17mg/L; p < 0.001) Table 2. The subgroup analysis of albuminuria status within the diabetic cohort showed even more differences (Table 3). Of the 75 diabetic participants, 43 (57.3%) had normo-albuminuria, while 32 (42.7%) had microalbuminuria. Although patients with normo-albuminuria had near-normal serum creatinine levels (0.97±0.17mg/dL), their cystatin C levels were already elevated (1.19 ± 0.22 mg/L). Microalbuminuria patients had even higher levels of cystatin C (1.49±0.27mg/L) as well as the subgroups difference between subgroups has been statistically significant (p<0.01). Level of serum creatinine is slightly higher in microalbuminuria subgroup (1.06 ± 0.21mg/dL), but difference has not been as significant as compared to that of cystatin C., as shown in Table 3.

Correlation analysis exposed statistically significant negative association between cystatin C as well as renal function (r=−0.72, p 0.001), compared with serum creatinine (r=-0.58, p=0.001), that has been greater with renal function decline. Table 4. This evidence implies that cystatin C can be utilised as more accurate biomarker of premature renal failure in patients with T2DM.

Table 1: Baseline Characteristics of Study Participants

Parameter	T2DM Patients (n = 75)	Controls (n = 75)	p-value
Age (years)	53.8 ± 6.4	52.9 ± 5.8	0.34
BMI (kg/m²)	27.2 ± 3.1	24.5 ± 2.7	<0.01
FPG (mg/dL)	158 ± 30	91 ± 10	<0.001
HbA1c (%)	8.1 ± 1.0	5.2 ± 0.3	<0.001

Table 2: Comparison of Renal Function Markers between Groups

Parameter	T2DM Patients (n = 75)	Controls (n = 75)	p-value
Serum Creatinine (mg/dL)	1.01 ± 0.20	0.88 ± 0.14	0.03
eGFR (mL/min/1.73 m²)	83.6 ± 13.8	99.2 ± 11.9	<0.001
UACR (mg/g)	39.8 ± 17.5	11.8 ± 4.9	<0.001
Cystatin C (mg/L)	1.32 ± 0.30	0.81 ± 0.17	<0.001

Table 3: Cystatin C and Creatinine Levels among Diabetic Subgroups

Subgroup	n (%)	Cystatin C (mg/L)	Serum Creatinine (mg/dL)
Normo-albuminuria	43 (57.3%)	1.19 ± 0.22	0.97 ± 0.17
Microalbuminuria	32 (42.7%)	1.49 ± 0.27	1.06 ± 0.21*

***p < 0.01 for cystatin C between subgroups**

Table 4: Correlation of Renal Markers (Pearson's Correlation with eGFR)

Marker	Correlation Coefficient (r)	p-value
Cystatin C	−0.72	<0.001
Creatinine	−0.58	<0.001

Discussion

Renal dysfunction in T2DM needs to be identified at very early stages to avoid irreversible nephron impairment and advancement to ESRD. In this case of 150 subjects (75 T2DM patients, and 75 HCs), the CysC levels have been significantly elevated in diabetic patients in comparison with the controls, despite the moderate increase in serum creatinine. It is noteworthy that normo-albuminuria patients also had increased cystatin C implying that renal destruction might occur earlier than it can be detected by microalbuminuria.

The rise in creatinine was low though eGFR had sharply fallen, highlighting the limited sensitivity of creatinine to early renal malfunction. The age, sex, mass of muscles, and nutrition influence creatinine levels and may confound the early glomerular filtration decline.

Contrary to this, cystatin C showed higher negative relationship with eGFR (r=-0.72) when comparing with creatinine (r=-0.58), this indicates its greater sensitivity. Similar conclusions were made by Dharnidharka et al. [14], who preferred to use cystatin C as the preferable moderate decline of GFR.

High cystatin C in diabetic individuals with non-albuminuria helps in validating the idea of early subclinical nephropathy. Similar outcomes have been indicated by Pucci et al. [15], insisted that the decline in glomerular filtration can go unnoticed before albumin excretion. Laterza et al. [16] also added that cystatin C offers more precise evaluation of the renal function because of its stable production and low extrarenal effects.

These findings indicate the rationale of having other biomarkers other than albuminuria to conduct early renal evaluation. Cystatin C has also been linked having an extended cardiometabolic risk. Shlipak et al. [17] stated that high cystatin C is a predictive factor of cardiovascular events and mortality independent of creatinine-based GFR.

Therefore, cystatin C can be utilised to observe patients at risk of cardiovascular diseases, also diagnose during early renal impairment. Similar diagnostic accuracy was observed by Perkins et al. [18] who emphasised that cystatin C can find early diabetic kidney disease and anticipate the regression of nephropathy with better glycemic control. Though historically microalbuminuria was viewed as initial clinical indicator of DN, [19], the renal involvement can be missed when using albuminuria as the reliance. Alicic et al. [20] outlined non-albuminuric progressions of diabetic kidney disease, which supported the application of cystatin C to identify it at an earlier stage. Such results have significant clinical implications.

Early renal impairment detection allows for timely adoption of reno-protective measures, among them being good glycemic and blood pressure regulation, renin-angiotensin-aldosterone system blockage, and more recent interventions, such as SGLT2 blockers. The use of cystatin C in daily check-ups can enhance cardiovascular and renal outcomes in T2DM.

Thus, CysC is both sensitive and useful in identifying early renal dysfunction in T2DM and can identify subtle GFR deterioration before the onset of obvious albuminuria or excessive rise in creatinine, which is why the use of CysC is beneficial tool in modern screening of DN.

Conclusion

CysC is highly sensitive and specific as initial sign of renal impairment in the patient having T2DM. Cystatin C detects small falls in the glomerular filtration rate sooner than serum creatinine, which remains normal until significant loss of nephrons has taken place. Our study indicated significantly elevated cystatin C levels in diabetic patients having normo-albuminuria and normal creatinine levels, which indicated its better results in identifying subclinical renal impairment. The association between eGFR and cystatin C is high, which makes it clinically relevant. Early diagnosis of renal impairment makes the therapeutic intervention timely and potentially slows the progression of more severe DN and ESRD. CysC that is regularly added to the routine procedures of diabetic screening could improve patient outcomes and risk assessment. More longitudinal studies are needed to prove its prognostic usefulness and cost-effectiveness in large populations.

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