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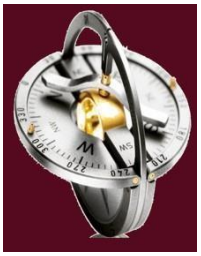

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Original Research

Use of Serum Cystatin C to Detect Early Decline of Glomerular Filtration Rate in Type-2 Diabetes Mellitus

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Abstract

Background: Diabetic nephropathy is a leading cause of end-stage renal disease. Early identification of renal impairment in type-2 diabetes is essential because structural damage becomes largely irreversible once overt nephropathy is established. Serum creatinine, the conventional marker used to estimate glomerular filtration rate (GFR), has a "blind range" in which substantial loss of GFR occurs before its concentration rises. Serum cystatin C has been proposed as an alternative marker that may detect early decline in GFR more reliably. ***Methods:*** This cross-sectional study was conducted over one year in the Postgraduate Department of Medicine, Government Medical College, Jammu. Eighty-one adults (30-80 years) with established type-2 diabetes mellitus were enrolled. Patients with baseline serum creatinine >1.4 mg/dL, known non-diabetic renal disease or conditions affecting urinary albumin excretion were excluded. Serum creatinine, serum cystatin C and urinary albumin were measured in all subjects. GFR was estimated using the Cockcroft -Gault equation and patients were classified into CKD stages I-III according to National Kidney Foundation guidelines. Correlations between GFR and both cystatin C and creatinine were analysed using Pearson's correlation coefficient. ***Results:*** The study included 47 males (58%) and 34 females (42%); mean age was 56.77 ± 11.35 years in males and 54.99 ± 11.44 years in females. Duration of diabetes ranged from 6 months to 17 years, with 66.7% having diabetes for <10 years. Overall, serum cystatin C showed a stronger negative correlation with GFR ($r = -0.776$; $R^2 = 0.602$; $p < 0.001$) than serum creatinine ($r = -0.511$; $R^2 = 0.260$; $p < 0.001$). In CKD stage II (GFR 60-89 ml/min/1.73 m²), elevated cystatin C was present in 39/45 patients (86.7%), whereas elevated creatinine was present in only 23/45 (51.1%). Cystatin C-GFR correlation remained strong in patients ≥65 years ($r = -0.6998$) and in both sexes (males $r = -0.7569$; females $r = -0.7595$), while creatinine-GFR correlation weakened in the elderly ($r = -0.3596$) and was lower, particularly in females ($r = -0.5032$). Cystatin C levels were increased in 90.0% of patients with m icroalbuminuria and 93.6% with macroalbuminuria, compared with 56.7% and 83.9% respectively for creatinine.

Keywords: *Serum Cystatin C, Glomerular Filtration Rate (GFR), Early renal dysfunction, Type-2 Diabetes Mellitus*

Introduction

Diabetic nephropathy has become one of the commonest causes of end-stage renal disease (ESRD) worldwide. Once clinically overt nephropathy is established, the course is typically one of progressive and often irreversible decline in renal function, with a high burden of cardiovascular morbidity and mortality. Early identification of renal involvement in type-2 diabetes therefore remains a major goal of clinical practice.

Routine assessment of renal function in diabetic patients relies on estimation of glomerular filtration rate (GFR) from serum creatinine. Creatinine, however, is influenced by muscle mass, age, sex and dietary intake. A substantial reduction in true GFR can occur before serum creatinine rises above the laboratory reference range, creating a "blind range" during which early diabetic kidney disease may be missed.

Cystatin C is a low molecular weight cysteine protease inhibitor produced at a constant rate by all nucleated cells. It is freely filtered at the glomerulus and is almost completely reabsorbed and catabolised in the proximal tubule, without tubular secretion. Because its production is largely independent of muscle mass, cystatin C has been proposed as a more sensitive endogenous marker of GFR that may detect early renal impairment, particularly in populations where creatinine performs poorly such as the elderly and women.

The present study was undertaken to evaluate the diagnostic performance of serum cystatin C relative to serum creatinine for early detection of diabetic nephropathy in patients with type-2 diabetes mellitus, with particular emphasis on correlation with estimated GFR, performance across CKD stages and influence of age, sex and albuminuric status.

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Materials and Methods

2.1 Study design and setting

This was a cross-sectional observational study conducted in the Postgraduate Department of Medicine, Government Medical College, Jammu, over a period of one year from November 2011 to October 2012.

2.2 Study population

Eighty-one consecutive patients with type-2 diabetes mellitus attending the medical outpatient department were enrolled. Age range was 30–80 years. All patients were known cases of type-2 diabetes with varying duration of disease.

2.3 Inclusion criteria

- Diagnosis of type-2 diabetes mellitus according to WHO criteria.
- Age between 30 and 80 years.
- Written informed consent to participate in the study.

2.4 Exclusion criteria

- Patients were excluded if they had any of the following:
- Baseline serum creatinine >1.4 mg/dL.
- Known non-diabetic renal disease (e.g. primary glomerulopathies, interstitial nephritis, obstructive uropathy).
- Long-standing uncontrolled hypertension or other conditions known to significantly influence urinary albumin excretion.
- Acute illness likely to affect renal function at the time of evaluation.

These criteria were applied to allow specific assessment of renal impairment attributable to diabetic nephropathy.

2.5 Clinical evaluation

A detailed history including duration of diabetes, treatment, comorbid illnesses and complications was obtained. Physical examination included measurement of blood pressure, body weight and height. Body mass index (BMI) was calculated as weight (kg)/height² (m²).

2.6 Laboratory investigations

- Morning fasting venous blood samples were collected for:
- Serum urea and creatinine: analysed using standard automated methods in the hospital laboratory.
- Serum cystatin C: estimated by a particle-enhanced immuno-turbidimetric assay as used in the institution's biochemistry department, with the laboratory reference range applied.

Morning urine specimens were subjected to routine examination and estimation of urinary albumin. Albumin excretion was used to classify subjects into:

- Normoalbuminuria (albumin excretion rate <30 mg/24 h)
- Microalbuminuria (30–299 mg/24 h)
- Macroalbuminuria (≥300 mg/24 h)

2.7 Estimation of GFR and CKD staging

Glomerular filtration rate was calculated for each patient using the Cockcroft-Gault formula based on serum creatinine, age, sex and body weight. On the basis of estimated GFR, subjects were categorised into CKD stages according to National Kidney Foundation (2002) guidelines:

Stage I: GFR ≥90 ml/min/1.73 m²

Stage II: GFR 60–89 ml/min/1.73 m²

Stage III: GFR 30–59 ml/min/1.73 m²

No patient in this series had GFR <30 ml/min/1.73 m².

2.8 Statistical analysis

Data were analysed using SPSS version 17 for Windows. Continuous variables were expressed as mean ± standard deviation (SD). Pearson's product-moment correlation coefficient (r) was used to evaluate linear relationships between serum cystatin C and GFR and between serum creatinine and GFR, overall and in subgroups defined by age, sex and albuminuric status. The coefficient of determination (R^2) was derived from r^2. A p value <0.05 was considered statistically significant.

Results

3.1 Baseline characteristics

Of the 81 patients studied, 47 were males (58.0%) and 34 were females (42.0%). Ages ranged from 30 to 80 years. Mean age in males was 56.77 ± 11.35 years and in females 54.99 ± 11.44 years. Duration of diabetes varied from 6 months to 17 years; 54 patients (66.7%) had diabetes for <10 years and 27 (33.3%) for ≥10 years.

Table 1: Age & Gender Distribution of Patients

Age group (in years)	Males No. (%)	Females No. (%)	Total No. (%)
<40	5(10.6)	5(14.7)	10(12.4)
41-50	9(19.2)	8(21.6)	17(20.0)
51-60	15(31.9)	10(29.4)	25(30.9)
61-70	11(23.4)	6(17.6)	17(20.0)
>70	7(14.9)	5(14.7)	12(14.8)
Total	**47**	**34**	**81**

Table 2: Duration of diabetes and gender distribution of patients

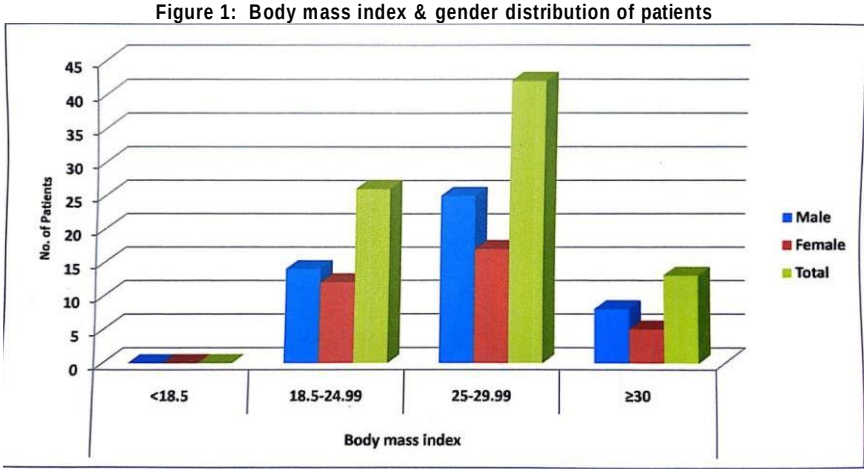
Duration of diabetes (years)	Males No. (%)	Females No. (%)	Total No. (%)
<10	33(70.2)	21(61.8)	54(66.7)
≥10	14(29.8)	13(38.2)	27(33.3)
Total	**47**	**34**	**81**

Most subjects were overweight; 51.9% had BMI 25-29.99 kg/m² and 16.0% had BMI ≥30 kg/m².
Serum triglycerides were ≥150 mg% in 56 patients (69.1%). Distribution of albuminuric status showed 30 patients (37.0%) with microalbuminuria, 20 (24.7%) with normoalbuminuria and 31 (38.3%) with macroalbuminuria.

Table 3: Body mass index, serum triglycerides and gender distribution of patients

BMI (kg/m²)	Males No. (%)	Females No. (%)	Total No. (%)
<18.5	0	0	0
18.5-24.99	14 (29.8)	12 (35.3)	26 (32.1)
25-29.99	25 (53.2)	17 (50.0)	42 (51.9)
≥30	8 (17.0)	5 (14.7)	13 (16.0)
Total	**47**	**34**	**81**
Serum triglycerides (mg%)	**Males No. (%)**	**Females No. (%)**	**Total No. (%)**
<150	12 (25.5)	13 (38.2)	25 (30.9)
≥150	35 (74.5)	21 (61.8)	56 (69.1)
Total	**47**	**34**	**81**

Figure 1: Body mass index & gender distribution of patients



3.2 Marker behaviour across CKD stages

Patients were grouped according to CKD stage based on estimated GFR. The proportions with elevated cystatin C and elevated creatinine in each stage are shown in Table 4.

Table 4: Levels of cystatin C, serum creatinine and various CKD stages, defined on the basis of GFR of the patients

Cystatin C levels	GFR (ml/min/1.73 m² BSA)*			
	30-59(III) No. (%)	**60-89(II) No. (%)**	**≥ 90 (I) No. (%)**	**Total No. (%)**
Increased	29(96.7)	39(86.7)	1(16.7)	69(85.2)
Normal	1(3.3)	6(13.3)	5(83.3)	12(14.8)
Total	**30**	**45**	**6**	**81**
Serum Creatinine levels	**GFR (ml/min/1.73 m² BSA)***			
Increased	27 (90.0)	23 (51.1)	0 (0.00)	50 (61.7)
Normal	3 (10.0)	22 (48.9)	6 (100)	31 (38.3)
Total	**30**	**45**	**6**	**81**

Elevated cystatin C was present in 69 of 81 patients (85.2%) overall, compared with elevated creatinine in 50 of 81 (61.7%). The difference in detection was most marked in CKD stage II, where nearly half of the patients would have been missed if screened by creatinine alone.

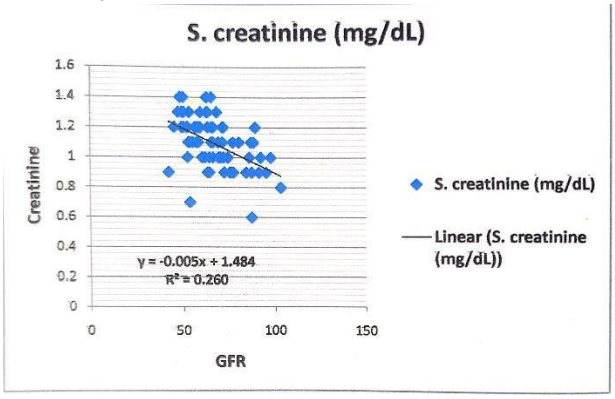
3.3 Correlation of markers with GFR

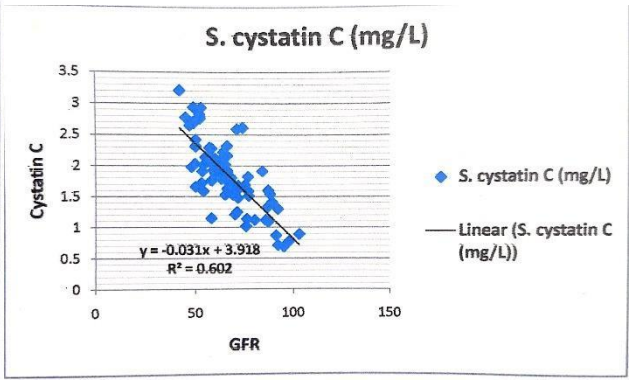
Overall, serum cystatin C showed a stronger negative correlation with GFR than serum creatinine:

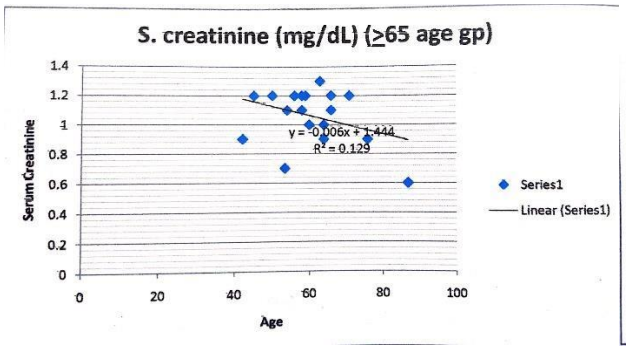
Table 5: Overall correlation of cystatin C with GFR and creatinine with GFR

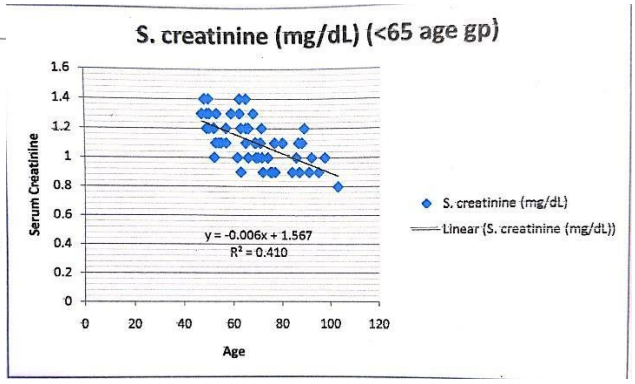
Coefficient of Correlation	Overall	≥ 65	<65
Serum cystatin C and GFR	-0.7760	-0.6998	-0.7761
Serum creatinine and GFR	-0.5107	-0.3596	-0.6406

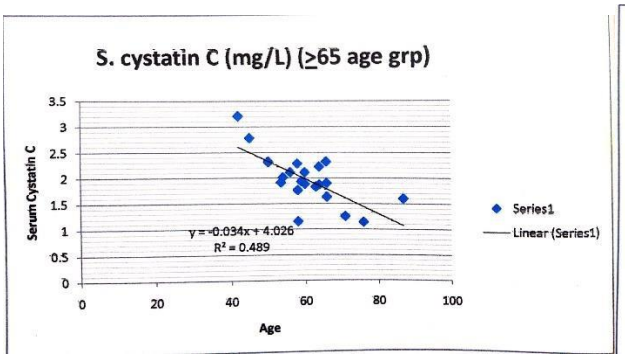
For cystatin C and GFR p = 0.001 (Highly significant); Coefficient of determination R = 0.602
For creatinine and GFR p = 0.001 (Highly significant); Coefficient of determination R = 0.260

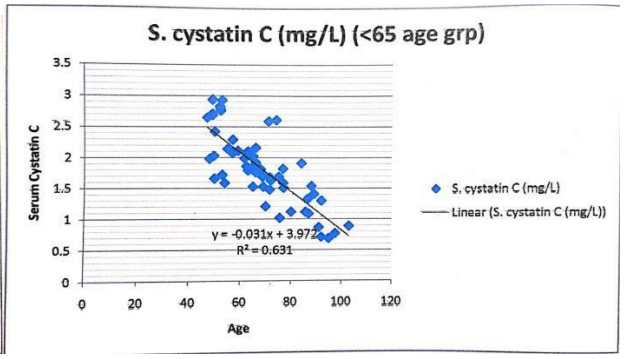












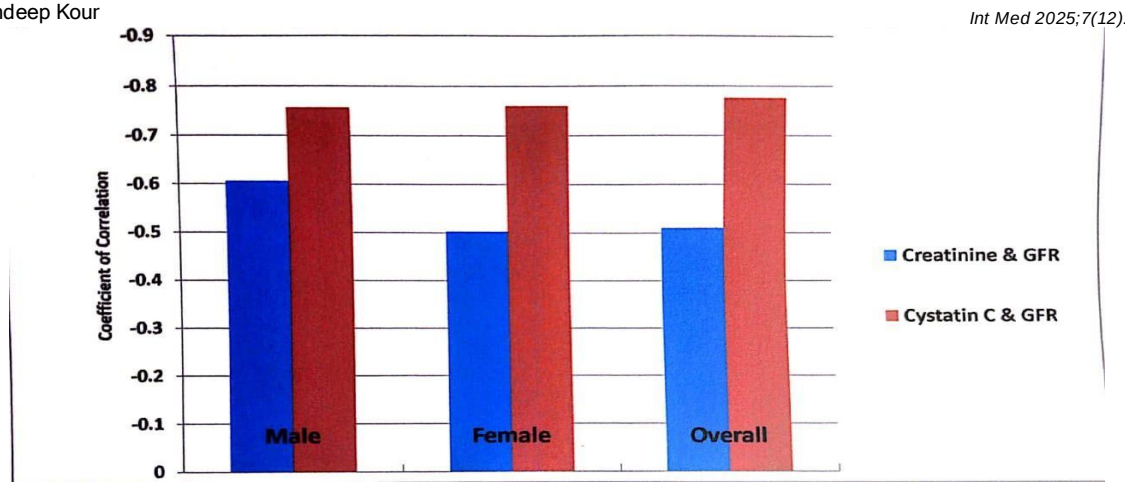
Thus, changes in cystatin C explained about 60% of the variation in GFR, whereas creatinine explained only about 26%. Coefficient of determination (R) for both cystatin C and creatinine with GFR, however, suggested that variation in GFR is explained more by change in cystatin concentration compared to creatinine. 'R' for cystatin C and GFR was 0.602 i.e. 60% of the variation of GFR can be explained by change in cystatin C concentration and 'R' for creatinine and GFR was 0.260 i.e. 26% of variation of GFR can be explained by change in creatinine concentration.
When analysed by age group, the correlation between creatinine and GFR weakened in older subjects, whereas the correlation for cystatin C remained strong.

3.5 Influence of gender
Gender-wise correlations are summarised in Table 6.

Table 6: Gender-wise correlation coefficients of cystatin C and creatinine with GFR

Coefficient of Correlation	Males	Females	Overall
Serum cystatin C and GFR	-0.7569	-0.7595	-0.7760
Serum creatinine and GFR	-0.6056	-0.5032	-0.5107

Cystatin C showed very similar strong negative correlations with GFR in both males and females. Creatinine correlations were weaker overall and particularly in females. For creatinine and GFR (r in males = -0.605, R = 36%; r in females = -0.503, R = 25%). As shown in the above table, similar correlation was found between males and females as far as cystatin C rise and GFR fall was concerned (r in males = -0.756, R = 57%; r in females = -0.789, R = 58%), whereas the relation between creatinine and GFR was slightly more stronger in males compared to females (r in males = -0.605, R = 36%; r in females = -0.503, R = 25%).



3.6 Relationship with albuminuria

Cystatin C and creatinine elevations were also examined in relation to albuminuric status.

Cystatin C was increased in 27 of 30 patients with microalbuminuria (90.0%), 15 of 20 with normoalbuminuria (75.0%) and 29 of 31 with macroalbuminuria (93.6%).

Creatinine was increased in 17 of 30 patients with microalbuminuria (56.7%), 9 of 20 with normoalbuminuria (45.0%) and 26 of 31 with macroalbuminuria (83.9%).

Table 7: Relationship of serum cystatin C levels and albuminuria

Serum cystatin C levels	Albuminuria		
	Micro No. (%)	Normo No. (%)	Macro No. (%)
Increased	27(90.0)	15(75.0)	29(93.6)
Normal	3(10.0)	5(25.0)	2(6.4)
Total	**30(37.0)**	**20(24.7)**	**31(38.3)**

Thus, cystatin C identified a higher proportion of patients with both micro- and macroalbuminuria than creatinine and showed elevation in a sizable proportion of patients who still had normoalbuminuria. As shown in the above table, a higher percentage of patients with microalbuminuria (90.0%) and macroalbuminuria (93.6%) were observed to have increased levels of cystatin C as compared to those having normoalbuminuria.

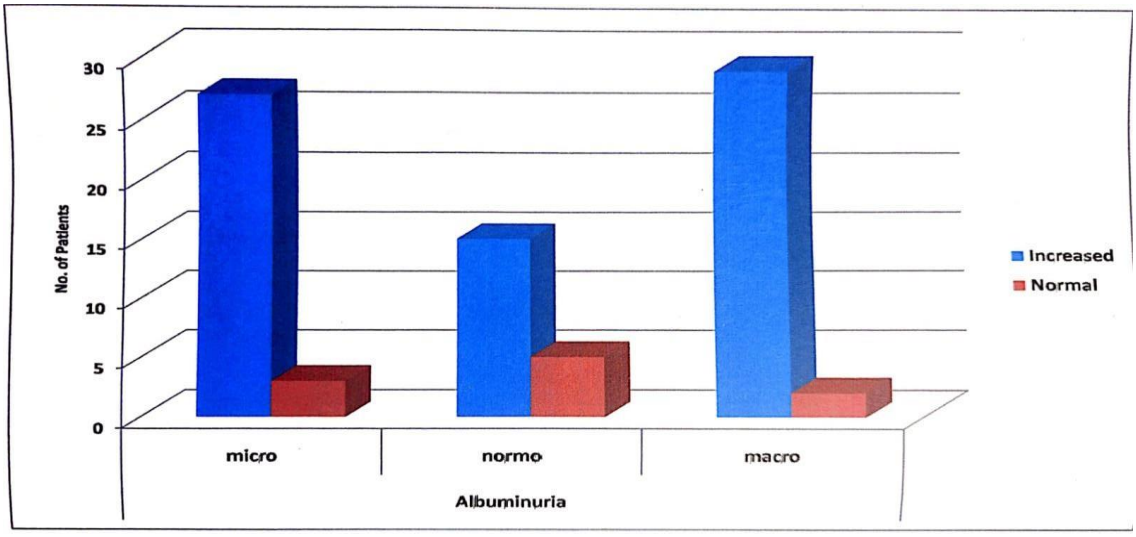
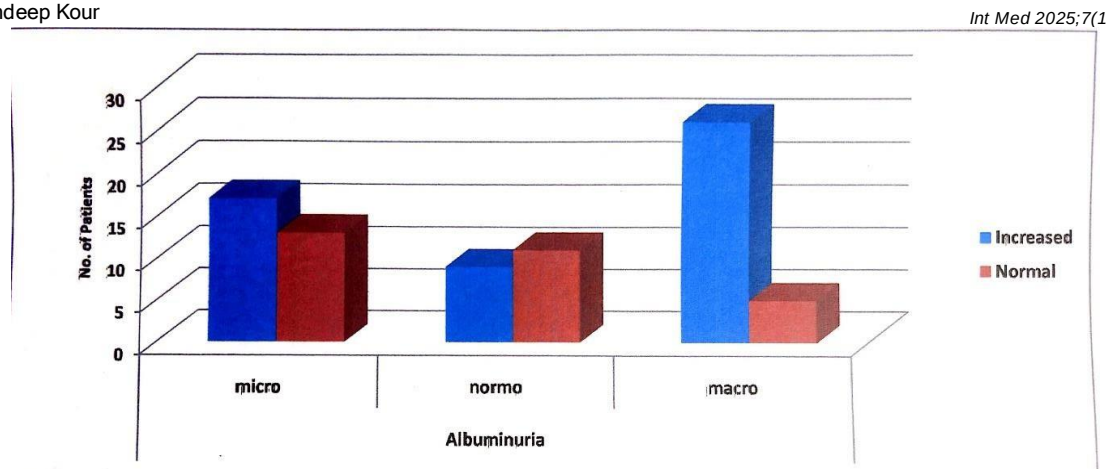


Table 8: Relationship of serum creatinine levels and albuminuria

Serum creatinine levels	Albuminuria		
	Micro No. (%)	Normo No. (%)	Macro No. (%)
Increased	17(56.7)	9(45.0)	26(83.9)
Normal	13(33.3)	11(55.0)	5(16.1)
Total	**30(37.0)**	**20(24.7)**	**31(38.3)**

As shown in the above table, a higher percentage of patients with macroalbuminuria (83.9%) and microalbuminuria (56.7%) were observed to have increased levels of creatinine as compared to those having normoalbuminuria, but the difference was less pronounced compared to cystatin C.



Discussion

This study evaluated serum cystatin C in comparison with serum creatinine as markers of renal function in adults with type-2 diabetes mellitus. The principal finding was that cystatin C showed a closer and stronger inverse relationship with estimated GFR than creatinine and detected early reduction in renal function more frequently, particularly in CKD stage II.

4.1 Early detection of reduced GFR

The marked difference between the two markers in CKD stage II illustrates the clinical importance of the creati nine “blind range”. In this study, cystatin C was elevated in 86.7% of patients with GFR 60-89 ml/min/1.73 m², whereas creatinine was elevated in only 51.1%. Patients in this range often have subclinical renal damage where early intervention may slow or halt progression. Relying solely on creatinine would therefore underestimate the true burden of diabetic kidney disease.

The stronger correlation of cystatin C with GFR ($r = -0.776$ vs -0.511 for creatinine) is consistent with reports that cystatin C is a more precise endogenous marker of GFR and that it increases with even small declines in filtration. Previous studies have shown similar findings in diabetic and non-diabetic populations, supporting the use of cystatin C for more accurate assessment of renal function.

4.2 Effect of age and sex

Creatinine production is closely linked to muscle mass, which is lower in women and decreases with age. This explains the los s of correlation between creatinine and GFR in elderly subjects in this study, and the generally weaker performance of creatinine i n females. In contrast, cystatin C is produced at a relatively constant rate by all nucleated cells and is much less affected by muscle mass. The pre sent data show that cystatin C retains a strong correlation with GFR in patients ≥65 years and in both sexes, supporting its use in older and female diabetic patients, in whom creatinine-based estimates are particularly unreliable.

4.3 Relationship with albuminuria

Microalbuminuria has long been used as an early marker of diabetic nephropathy. In this study, cystatin C was elevated in 90% of patients with microalbuminuria and in almost three-quarters of those who still had normoalbuminuria, while creatinine was elevated in only about half of microalbuminuric patients and fewer normoalbuminuric patients. This suggests that cystatin C may detect functional impairment either earlier than, or at least in parallel with, the onset of microalbuminuria and may add diagnostic value when albumin excretion is still within the normal range.

4.4 Limitations

This was a single-centre study with a relatively small sample size and cross-sectional design, so temporal relationships and prognostic value could not be assessed. GFR was estimated using the Cockcroft-Gault equation rather than measured directly, which may introduce some inaccuracy. Urinary albumin excretion was assessed using a single sample rather than timed collections or repeated measurements. Cost and availability of cystatin C assays may also limit immediate widespread use, particularly in resource-limited settings.

Nevertheless, the consistency of findings across CKD stages, age and gender groups, together with concordance with published work, support the conclusion that cystatin C offers real clinical advantages over creatinine in this patient population.

Conclusion

Serum cystatin C is a more sensitive and more strongly GFR-related marker than serum creatinine for detecting early renal impairment in patients with type-2 diabetes mellitus. It detects a substantially higher proportion of patients with mild reductions in GFR, maintains good performance in elderly subjects and in both sexes, and correlates well with albuminuric status. Incorporation of cystatin C measurement into routine evaluation of diabetic patients, particularly those at high risk for nephropathy, may allow earlier diagnosis and closer monitoring of renal function than is possible with creatinine alone.

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