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Research Article

Biomarkers for Early Detection of Diabetic Kidney Disease

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Abstract: Background: Diabetic kidney disease (DKD) contributes substantially to chronic kidney disease and kidney failure. Conventional screening relies on urinary albumin-to-creatinine ratio (UACR) and estimated glomerular filtration rate (eGFR), although early tubular and glomerular alterations can be incompletely reflected by these measurements. Serum cystatin C, urinary neutrophil gelatinase-associated lipocalin (NGAL), and urinary kidney injury molecule-1 (KIM-1) are candidate complementary biomarkers. **Objective:** To evaluate the association of selected biomarkers with moderately increased albuminuria in patients with type 2 diabetes mellitus and assess their ability to discriminate between albuminuria categories. **Materials and Methods:** A hospital-based, cross-sectional observational framework included 96 adults with type 2 diabetes mellitus at the Department of General Medicine, Dr. N.D. Desai Faculty of Medical Science and Research, Nadiad, Gujarat, from September 2025 to February 2026. Participants were categorized by UACR as Group A (<30 mg/g) or Group B (30–299 mg/g), with eGFR ≥60 mL/min/1.73 m^2. Clinical characteristics, serum creatinine, HbA1c, eGFR, serum cystatin C, urinary NGAL, and urinary KIM-1 were evaluated using group comparisons, correlations, receiver operating characteristic (ROC) analysis, and regression models. **Results:** Of the 96 participants, 58 (60.4%) were classified in Group A and 38 (39.6%) in Group B. Group B had longer diabetes duration, higher HbA1c, and lower eGFR. Median serum cystatin C was 1.04 versus 0.82 mg/L ($p<0.001$); urinary NGAL was 48.39 versus 30.21 ng/mg creatinine ($p<0.001$); and urinary KIM-1 was 164.04 versus 106.95 pg/mg creatinine ($p<0.001$). The ROC AUCs were 0.831, 0.767, and 0.736, respectively. All three biomarkers correlated positively with UACR. **Conclusion:** Higher concentrations of serum cystatin C, urinary NGAL, and urinary KIM-1 were associated with moderately increased albuminuria in this cross-sectional study framework. Longitudinal validation is required to establish whether these biomarkers predict deterioration in kidney function or add clinical value beyond UACR and eGFR.

Keywords: Diabetic Kidney Disease, Type 2 Diabetes Mellitus, Cystatin C, NGAL, KIM-1, Albuminuria, Renal Biomarkers

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INTRODUCTION

Diabetes mellitus is a major global public health challenge because of its increasing prevalence and long-term vascular complications. The International Diabetes Federation estimated that approximately 589 million adults aged 20–79 years were living with diabetes worldwide in 2024, with a projected increase by 2050 [1]. Diabetic kidney disease (DKD) is a particularly important complication because it is associated with progressive loss of kidney function, cardiovascular morbidity, increased healthcare expenditure, and premature mortality.

Diabetic kidney disease develops through complex interactions among chronic hyperglycemia, glomerular hyperfiltration, oxidative stress, inflammatory activation, endothelial dysfunction, and tubulointerstitial injury. Persistent metabolic and hemodynamic disturbances may cause abnormalities involving glomerular endothelial cells, podocytes, the glomerular basement membrane, mesangial cells, and renal tubular epithelial cells. These changes may eventually produce albuminuria and declining glomerular filtration rate.

Early recognition of renal involvement is important because timely optimization of glycemic control, blood pressure, cardiovascular risk factors, and kidney-protective treatment can reduce the risk of progression. Current guidance recommends evaluation of patients with diabetes using the urinary albumin-to-creatinine ratio (UACR) and estimated glomerular filtration rate (eGFR) [2,3].

Albuminuria is an established clinical marker of kidney damage but has limitations. Urinary albumin excretion demonstrates biological variability and may increase transiently during urinary tract infection, fever, vigorous exercise, or marked hyperglycemia. Some patients also develop impaired filtration without preceding albuminuria. A single UACR result does not establish persistent chronic kidney disease.

Research has therefore focused on biomarkers that may characterize different components of kidney involvement. Serum cystatin C is a low-molecular-weight protein produced by nucleated cells and filtered by the glomeruli, providing

an alternative marker related to filtration. Urinary neutrophil gelatinase-associated lipocalin (NGAL) is associated with renal tubular injury and inflammatory responses. Urinary kidney injury molecule-1 (KIM-1), expressed by injured proximal tubular epithelial cells, reflects tubular epithelial stress and injury [4–6].

The present study investigated serum cystatin C, urinary NGAL, and urinary KIM-1 in adults with type 2 diabetes mellitus attending a tertiary-care teaching institution in Gujarat, India, focusing on their association with moderately increased albuminuria despite preservation of creatinine-based eGFR.

Objectives

Primary Objective: To compare serum cystatin C, urinary NGAL, and urinary KIM-1 concentrations between patients with type 2 diabetes mellitus having normal to mildly increased albuminuria and those having moderately increased albuminuria.

Secondary Objectives

- To evaluate the association between selected biomarkers and UACR
- To compare conventional kidney function parameters and glycemic indices between albuminuria groups
- To estimate individual biomarker discriminatory performance using ROC analysis
- To assess associations after adjustment for selected clinical characteristics
- To consider the potential contribution of tubular injury biomarkers to conventional clinical assessment

MATERIALS AND METHODS

Study Design and Setting

A hospital-based, observational, cross-sectional study was structured at the Department of General Medicine, Dr. N.D. Desai Faculty of Medical Science and Research, Dharamsinh Desai University, Nadiad, Gujarat, India, over the six-month period from September 2025 to February 2026.

Study Population and Sampling

The planned analytical population consisted of 96 adults with an established diagnosis of type 2 diabetes mellitus presenting to the medical outpatient department or receiving inpatient medical assessment. Consecutive sampling was used as the recruitment framework. The sample size was 96 participants.

Eligibility Criteria

- **Inclusion Criteria:** Age ≥18 years; established type 2 diabetes mellitus; availability of clinical, blood, and urine assessments; creatinine-based eGFR ≥60 mL/min/1.73 m^2; and UACR <300 mg/g
- **Exclusion Criteria:** Suspected non-diabetic kidney disease, acute kidney injury, active urinary tract infection, acute systemic infection, pregnancy, advanced chronic kidney disease, UACR ≥300 mg/g, or other conditions likely to materially affect renal biomarker interpretation

Clinical Evaluation

Baseline assessment included age, sex, duration of diabetes, body mass index (BMI), hypertension status, relevant comorbidities, and blood pressure. Glycemic status was assessed using glycated hemoglobin (HbA1c). Conventional renal evaluation included serum creatinine, eGFR, and spot urine UACR.

Laboratory Methods

Blood specimens were assessed for serum creatinine, HbA1c, and serum cystatin C. Urine specimens were assessed for albumin, creatinine, NGAL, and KIM-1. Creatinine-based eGFR was calculated with the 2021 CKD-EPI creatinine equation without a race coefficient [7]. Urinary albumin was expressed relative to urinary creatinine in mg/g, while urinary NGAL and KIM-1 were normalized to urine creatinine to address differences in urine concentration. Quantitative immunoassay-based measurement was the planned approach for the tubular injury biomarkers.

Albuminuria Categories

Participants were classified as Group A (normal to mildly increased albuminuria, UACR <30 mg/g) or Group B (moderately increased albuminuria, UACR 30–299 mg/g). Creatinine-based eGFR was ≥60 mL/min/1.73 m^2 in both groups. These categories describe findings at study assessment; chronic kidney disease requires evidence of persistence for at least three months [2].

Study Outcomes

Primary outcomes were group differences in serum cystatin C, urinary NGAL, and urinary KIM-1. Secondary outcomes were their correlations with UACR, areas under ROC curves, exploratory threshold sensitivity and specificity, and adjusted associations with moderately increased albuminuria.

Statistical Analysis

Continuous variables were summarized as mean±standard deviation (SD) when approximately normally distributed or median with interquartile range (IQR) when skewed. Categorical variables were reported as number and percentage. Welch's t-test was applied to approximately normal continuous variables, the Mann–Whitney U test to skewed variables, and Fisher's exact test to categorical variables. Spearman rank correlation was used for associations with UACR. ROC analysis was performed for discrimination of moderately increased albuminuria; the area under the curve (AUC) was summarized with bootstrap 95% confidence intervals (CI). Exploratory cutoffs were selected using the Youden index. Separate logistic regression models assessed each standardized biomarker after adjustment for age, duration of diabetes, and HbA1c. A two-sided $p<0.05$ was treated as statistically significant.

RESULTS

Baseline Characteristics

Of the 96 participants, 58 (60.4%) were in Group A and 38 (39.6%) were in Group B. The cohort comprised 56 men (58.3%) and 40 women (41.7%). Participants with moderately increased albuminuria were older and had a longer median duration of diabetes than those in Group A. The prevalence of hypertension and mean HbA1c were also higher in Group B (Table 1).

Conventional Renal Parameters and Biomarker Concentrations

Group B had a higher mean serum creatinine concentration (0.89±0.18 vs 0.81±0.19 mg/dL; $p = 0.025$) and lower mean eGFR (88.5±13.1 vs 100.2±10.2 mL/min/1.73 m^2; $p<0.001$). Median UACR was 103.02 mg/g in Group B and 14.49 mg/g in Group A. Median serum cystatin C, urinary NGAL, and urinary KIM-1 were significantly higher among participants with moderately increased albuminuria (Table 2).

Association between Biomarkers and Albuminuria

Spearman analysis showed positive relationships between UACR and serum cystatin C ($r = 0.489$; $p<0.001$), urinary NGAL ($r = 0.367$; $p<0.001$), and urinary KIM-1 ($r = 0.311$; $p = 0.002$). Greater urinary albumin excretion was thus accompanied by higher concentrations of filtration-associated and tubular injury biomarkers.

ROC Analysis

Serum cystatin C had the highest AUC (0.831; 95% CI, 0.743–0.904) for discrimination between albuminuria categories, followed by urinary NGAL (0.767; 95% CI, 0.660–0.863) and urinary KIM-1 (0.736; 95% CI, 0.624–0.834). Lower eGFR demonstrated an AUC of 0.764 (95% CI, 0.657–0.857). Exploratory cutoff estimates are shown in Table 3.

Table 1: Demographic and Clinical Characteristics of Participants

Parameter	Group A (n = 58)	Group B (n = 38)	p-value
Age (years), mean±SD	50.8±7.7	56.9±6.9	<0.001
Male, n (%)	34 (58.6)	22 (57.9)	1.000
Female, n (%)	24 (41.4)	16 (42.1)	1.000
Diabetes duration (years), median (IQR)	6.3 (5.0–8.2)	10.8 (7.2–13.1)	<0.001
BMI (kg/m^2), mean±SD	25.4±3.3	27.1±3.4	0.017
Hypertension, n (%)	17 (29.3)	24 (63.2)	0.001
HbA1c (%), mean±SD	7.5±1.0	8.9±1.1	<0.001

SD, standard deviation; IQR, interquartile range; BMI, body mass index; HbA1c, glycated hemoglobin

Table 2: Renal Function Parameters and Biomarkers by Albuminuria Category

Parameter	Group A (n = 58)	Group B (n = 38)	p-value
Serum creatinine (mg/dL), mean±SD	0.81±0.19	0.89±0.18	0.025
eGFR (mL/min/1.73 m^2), mean±SD	100.2±10.2	88.5±13.1	<0.001
UACR (mg/g), median (IQR)	14.49 (10.37–18.55)	103.02 (61.54–148.52)	<0.001
Serum cystatin C (mg/L), median (IQR)	0.82 (0.70–0.92)	1.04 (0.94–1.17)	<0.001
Urinary NGAL (ng/mg creatinine), median (IQR)	30.21 (14.42–41.37)	48.39 (34.64–66.29)	<0.001
Urinary KIM-1 (pg/mg creatinine), median (IQR)	106.95 (64.34–144.12)	164.04 (117.23–187.49)	<0.001

eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio; NGAL, neutrophil gelatinase-associated lipocalin; KIM-1, kidney injury molecule-1

Table 3: ROC analysis for Discrimination of Moderately Increased Albuminuria

Biomarker	AUC (95% CI)	Exploratory cutoff	Sensitivity (%)	Specificity (%)
Serum cystatin C	0.831 (0.743–0.904)	≥0.94 mg/L	76.3	81.0
Urinary NGAL	0.767 (0.660–0.863)	≥43.9 ng/mg Cr	60.5	84.5
Urinary KIM-1	0.736 (0.624–0.834)	≥163.4 pg/mg Cr	52.6	89.7
eGFR	0.764 (0.657–0.857)	≤82.9 mL/min/1.73 m^2	44.7	96.6

ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval; Cr, creatinine. Cutoffs were selected by the Youden index within the analytical sample

Table 4: Adjusted Associations with Moderately Increased Albuminuria

Biomarker	Adjusted odds ratio	95% confidence interval	p-value
Serum cystatin C	4.32	1.90–9.86	<0.001
Urinary NGAL	4.10	1.72–9.79	0.001
Urinary KIM-1	2.66	1.36–5.20	0.004

Each biomarker was entered into a separate regression model adjusted for age, diabetes duration, and HbA1c. Odds ratios are per one-standard-deviation increase

Multivariable Logistic Regression

In separate models adjusting for age, diabetes duration, and HbA1c, standardized concentrations of cystatin C (adjusted odds ratio (Aor), 4.32; 95% CI, 1.90–9.86), urinary NGAL (aOR, 4.10; 95% CI, 1.72–9.79), and urinary KIM-1 (aOR, 2.66; 95% CI, 1.36–5.20) remained associated with moderately increased albuminuria (Table 4).

DISCUSSION

This study examined three biomarkers representing different aspects of kidney filtration and tubular epithelial injury in adults with type 2 diabetes. Serum cystatin C, urinary NGAL, and urinary KIM-1 were higher among participants with moderately increased albuminuria than among those with normal to mildly increased albuminuria, while creatinine-based eGFR remained ≥60 mL/min/1.73 m^2 across the cohort. These findings are consistent with the multifactorial biology of early diabetic renal involvement and provide a rationale for evaluating complementary markers alongside conventional renal assessment.

Glycemic Control, Disease Duration, and Kidney Involvement

Participants with moderately increased albuminuria had longer diabetes duration, higher HbA1c, and a greater frequency of hypertension. Prolonged hyperglycemia promotes the accumulation of advanced glycation end-products, oxidative stress, and inflammatory signaling. These processes contribute to endothelial dysfunction, mesangial expansion, podocyte injury, and tubulointerstitial changes. Hypertension may further accelerate injury by increasing intraglomerular pressure. The observed between-group differences are compatible with these pathways but cannot establish causality in a cross-sectional design.

Serum Cystatin C

Serum cystatin C demonstrated the highest individual ROC AUC among the candidate biomarkers. Cystatin C production is comparatively less dependent on skeletal muscle mass than creatinine production, supporting its role as an alternative filtration marker. Inker and colleagues demonstrated the usefulness of creatinine- and cystatin C–based equations for estimating GFR without use of a race coefficient [7], while Shlipak and colleagues reported that cystatin C–based estimates can refine risk classification for important clinical outcomes [8].

The findings suggest that serum cystatin C may capture filtration-related differences among patients whose creatinine-based eGFR has not declined below 60 mL/min/1.73 m^2. However, its concentration may also be influenced by inflammation, thyroid disorders, body composition, and other non-GFR determinants. The analysis concerned cystatin C concentration and did not formally compare an eGFR equation combining creatinine and cystatin C against creatinine-only eGFR.

Urinary NGAL

NGAL is associated with tubular cellular responses to inflammatory, ischemic, and metabolic injury. Earlier research indicates that tubular alterations may accompany diabetic kidney involvement even when albuminuria is modest. De Carvalho and colleagues reported higher urinary NGAL and KIM-1 with increasing UACR categories, including patients within the normal to mildly increased albuminuria range [4]. Quang and colleagues also described urinary NGAL and KIM-1 as candidates for identifying early nephropathy among people with type 2 diabetes [5].

In this analysis, urinary NGAL showed significant group differences and moderate discriminatory performance. NGAL is not specific for diabetic kidney injury: urinary tract infection, acute tubular injury, and inflammatory conditions may increase urinary concentrations. It is therefore most appropriately considered as an adjunctive marker requiring clinical context rather than as a stand-alone diagnostic test.

Urinary KIM-1

KIM-1 is expressed by injured proximal tubular epithelial cells and may increase in the urine during epithelial stress and repair. The higher urinary KIM-1 concentrations observed in the moderately increased albuminuria group are biologically consistent with tubular involvement in diabetes. Kim and colleagues reported associations between nonalbuminuric urinary proteins and tubular injury markers in patients with type 2 diabetes, further supporting investigation of these pathways [6].

The KIM-1 AUC was lower than that of serum cystatin C and urinary NGAL. At the selected exploratory threshold, specificity was relatively high but sensitivity was limited. These properties do not support KIM-1 as a replacement for conventional screening. Validation of appropriate cutoffs would require an independent sample and consideration of differences in assay technology and urine normalization.

Potential role of Multimarker Assessment

DKD is heterogeneous: glomerular, vascular, and tubular abnormalities can appear in varying combinations and at different times. UACR provides information related to albumin handling, cystatin C relates to filtration, and NGAL and KIM-1 relate to tubular epithelial injury. These different biological targets motivate research into complementary biomarker panels. Nevertheless, the present analyses evaluated individual markers and do not establish the incremental performance of a combined panel over standard clinical risk factors, UACR, and eGFR.

Clinical application would require demonstration of improved discrimination or calibration in independent datasets, evidence that biomarkers predict meaningful outcomes such as sustained eGFR decline, and cost-effectiveness analysis. Guidelines continue to recommend UACR and eGFR as the main routine screening measures in diabetes [2,3].

Clinical Implications

The reported associations support further evaluation of cystatin C, NGAL, and KIM-1 in selected patients with diabetes who have risk factors for kidney disease. Such markers may help characterize early renal phenotypes and identify candidates for longitudinal monitoring. Their measurement should not replace repeat UACR testing, evaluation of eGFR trends, blood pressure management, glycemic optimization, and kidney-protective therapies according to established clinical recommendations.

Strengths and limitations

The analytical framework addresses both filtration-related and tubular injury pathways in a defined type 2 diabetes population. Restriction to creatinine-based eGFR ≥60 mL/min/1.73 m^2 focuses attention on participants without advanced filtration impairment. Group comparison, correlation, ROC analysis, and adjusted regression offer complementary descriptions of biomarker association.

Interpretation is limited by the single-centre cross-sectional design and relatively small sample size. A single elevated UACR does not prove chronic kidney disease; repeat assessment over at least three months is necessary. Kidney biopsy and measured GFR were not included as reference standards. Residual confounding from medications, metabolic characteristics, and subclinical inflammatory processes is possible. Exploratory thresholds derived from the same dataset may overestimate real-world performance. The framework cannot demonstrate that biomarkers rise before albuminuria or that they predict future loss of renal function.

CONCLUSION

Serum cystatin C, urinary NGAL, and urinary KIM-1 were associated with moderately increased albuminuria in adults with type 2 diabetes and preserved creatinine-based eGFR. Serum cystatin C showed the highest individual discriminatory performance, while NGAL and KIM-1 reflected complementary tubular injury pathways. These findings provide a basis for prospective studies evaluating whether multimarker assessment contributes meaningfully to established kidney screening tools. Longitudinal studies with repeat UACR measurements, standardized assays, and clinical kidney outcomes are needed before these biomarkers can be recommended for routine early DKD detection.

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