

Systematic Review Article

EMERGING BIOMARKERS FOR THE EARLY DETECTION AND PROGRESSION OF DIABETIC KIDNEY DISEASE: A SYSTEMATIC REVIEW

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ABSTRACT

Background: Diabetic kidney disease (DKD) is a major microvascular complication of diabetes and a leading cause of chronic kidney disease and end-stage kidney disease. Early detection is crucial, as renal injury may develop before abnormalities in conventional markers such as estimated glomerular filtration rate (eGFR) and urinary albumin-to-creatinine ratio (UACR). Emerging biomarkers, including kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), cystatin C, N-acetyl- β -D-glucosaminidase (NAG), liver-type fatty acid-binding protein (L-FABP), inflammatory and tubular injury markers, and proteomic/metabolomic signatures, may improve early detection and prediction of DKD progression. However, evidence regarding their diagnostic and predictive value remains heterogeneous. **Objectives:** The study aims to identify and evaluate emerging biomarkers for early detection and progression of DKD, assess their diagnostic performance, compare them with conventional markers such as UACR and eGFR, and determine the most promising biomarkers while identifying gaps for future research.

Materials and Methods: This systematic review was conducted in accordance with the PRISMA guidelines. A comprehensive literature search was performed using PubMed/MEDLINE, Scopus, Web of Science, Embase, Cochrane Library, and Google Scholar. Relevant keywords such as Diabetic kidney disease, Emerging biomarkers, Diagnostic biomarkers, Kidney injury molecule-1, Neutrophil gelatinase-associated lipocalin, Cystatin C, Tubular injury biomarkers, Proteomics, Metabolomics were used. Original research studies, including cohort, case-control, cross-sectional, randomized controlled trials, case report studies evaluating emerging biomarkers for early detection and progression of DKD in adults with diabetes were included. Articles published from the year 2012 were included in results. Study selection involved title and abstract screening followed by full-text assessment, with the process documented using a PRISMA flow diagram. Findings were synthesized narratively.

Results: The identified biomarkers included urinary proteomic and metabolomic signatures, podocyte-associated markers, tubular injury markers, inflammatory mediators, and circulating proteins. Urinary proteomic signatures, particularly the Chronic Kidney Disease 273 (CKD273) classifier, demonstrated strong potential for predicting progression from normoalbuminuria to microalbuminuria or macroalbuminuria, with reported area under the curve (AUC) values of approximately 0.93. Several biomarkers, including podocalyxin, kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), cystatin C, and angiopoietin-like protein-4, were significantly associated with albuminuria, reduced estimated glomerular filtration rate (eGFR), or early tubular and podocyte injury. Circulating tumor necrosis factor receptors 1 and 2 (TNFR-1 and TNFR-2) were consistently

associated with subsequent eGFR decline and progression to end-stage renal disease. Emerging multi-biomarker and omics-based panels demonstrated improved diagnostic and prognostic performance, with reported AUC values ranging from 0.81 to 0.99. Recent studies identified promising candidates such as serpin family A member 1 (SERPINA1), urinary podocalyxin, branched-chain amino acids, and combined urinary protein panels, highlighting their potential for earlier detection and risk stratification of diabetic kidney disease.

Conclusion: Emerging urinary, circulating, proteomic, metabolomic, and multi-biomarker panels show promise for early DKD detection and progression prediction beyond conventional markers. Large, multicenter longitudinal studies are needed for validation and clinical implementation.

Keywords: Diabetic kidney disease, Emerging biomarkers, Diagnostic biomarkers, Kidney injury molecule-1, Neutrophil gelatinase-associated lipocalin, Cystatin C, Tubular injury biomarkers, Proteomics, Metabolomics.

INTRODUCTION

Diabetic kidney disease (DKD) is a common microvascular complication of diabetes mellitus and a major contributor to chronic kidney disease and end-stage kidney disease worldwide. Early identification of DKD is important because renal structural and functional abnormalities can develop before significant changes are detected by conventional markers such as estimated glomerular filtration rate (eGFR) and urinary albumin-to-creatinine ratio (UACR). Singh A et al. (2026) concluded that while mortality and renal outcomes were comparable between groups, diabetic patients with acute kidney injury (AKI) were significantly older and had a higher prevalence of chronic kidney disease (CKD) and hypertension ($P < 0.001$) than non-diabetic patients.^[1]

Emerging biomarkers, including kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), cystatin C, N-acetyl- β -D-glucosaminidase (NAG), liver-type fatty acid-binding protein (L-FABP), inflammatory and tubular injury markers, as well as proteomic and metabolomic signatures, have demonstrated potential for detecting early renal injury. These biomarkers may provide additional information about renal tubular damage, inflammation, and other pathological processes that may not be identified by conventional measures.

Colhoun HM & Marcovecchio ML (2018) reviewed prognostic biomarkers for DKD, highlighting that albuminuria and eGFR remain useful predictors. Although numerous novel protein, lipid, and metabolite biomarkers show potential, their clinical utility requires validation beyond established risk factors.^[2]

Fiseha T & Tamir Z (2016) highlighted that urinary tubular injury markers may detect diabetic nephropathy before microalbuminuria develops. These include neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), liver-type fatty acid-binding protein (L-FABP), N-acetyl- β -glucosaminidase (NAG), alpha-1-microglobulin (A1M), beta-2-microglobulin (B2-M), and retinol-binding protein (RBP), which may

improve early detection of normoalbuminuric diabetic nephropathy.^[3]

Porrini E et al. (2015) highlighted that diabetic kidney disease progresses variably, with GFR decline potentially occurring before overt albuminuria. Factors such as hypertension, obesity, dyslipidaemia, female sex, and glomerular hyperfiltration may accelerate renal deterioration, particularly in type 2 diabetes, emphasizing the need for individualized management.^[4]

Gembillo G et al. (2026) highlighted the potential of urinary biomarkers for early detection, monitoring, and risk stratification of diabetic kidney disease. Markers such as albumin, KIM-1, and NGAL, along with urinary metabolomic and genetic signatures, may improve early diagnosis and enable more personalized DKD management.^[5]

However, their diagnostic and predictive performance has varied across studies, and their clinical utility remains uncertain. Therefore, this systematic review aims to synthesize the available evidence on emerging biomarkers and assess their potential role in the early detection and risk stratification of DKD.

Objectives

The study aims to identify emerging biomarkers for the early detection and progression of diabetic kidney disease (DKD), evaluate their diagnostic performance, and compare their utility with conventional markers such as urinary albumin-to-creatinine ratio (UACR) and estimated glomerular filtration rate (eGFR). It will also determine the most promising biomarkers for early DKD detection and highlight existing evidence gaps to guide future research.

MATERIALS AND METHODS

This systematic review was conducted in accordance with the PRISMA guidelines and searched PubMed/MEDLINE, Scopus, Web of Science, Embase, Cochrane Library, and Google Scholar using relevant keywords such as Diabetic kidney disease, Emerging biomarkers, Diagnostic biomarkers, Kidney injury molecule-1, Neutrophil gelatinase-associated lipocalin, Cystatin C, Tubular

injury biomarkers, Proteomics, Metabolomics. Eligible study designs included original research studies, randomized controlled trials, cohort studies, cross-sectional studies, case-control studies, comparative observational studies, case reports evaluating emerging biomarkers for the early detection and progression of DKD in patients with diabetes mellitus. Studies without sufficient or extractable outcome data, studies not directly evaluating biomarkers for early DKD detection, conference abstracts, editorials, letters were excluded. Articles published from the year 2012 were included in results. Titles, abstracts, and full-text articles were screened independently by two reviewers, with disagreements resolved through discussion. Data extraction and quality assessment were performed independently using standardized forms and appropriate tools according to study design. Extracted data included biomarker type, study population, diagnostic criteria, biomarker levels, sensitivity, specificity, predictive values, AUC/ Receiver Operating Characteristic (ROC), and comparisons with conventional markers such as UACR and eGFR. Due to heterogeneity in biomarker types, study designs, populations, and outcome reporting, the findings were synthesized narratively.

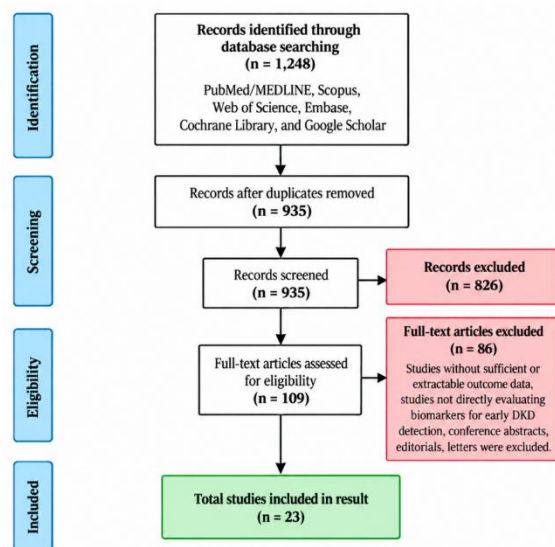


Figure 1: PRISMA Flow chart of Study Selection Process

RESULTS

Zürbig P et al. (2012) assessed urinary proteomics in 35 patients with type 1 or 2 diabetes. A Chronic Kidney Disease (CKD) peptide classifier predicted progression to macroalbuminuria up to 5 years earlier than urinary albumin (Area Under the Curve [AUC] 0.93 vs. 0.67). Collagen fragments were key biomarkers 3–5 years before progression, supporting urinary proteomics as an early non-invasive predictor of diabetic nephropathy.^[6]

Tofte N et al. (2020) evaluated CKD273 for predicting microalbuminuria in 1,775 patients with

type 2 diabetes and normoalbuminuria. High-risk CKD273 scores were associated with greater progression to microalbuminuria (28% vs. 9%; Hazard Ratio [HR] 2.48, 95% Confidence Interval [CI] 1.80–3.42; $p < 0.0001$) and impaired renal function (HR 3.50, 95% CI 2.50–4.90). Spironolactone did not significantly reduce microalbuminuria (25% vs. 33%; HR 0.81, 95% CI 0.49–1.34; $p = 0.41$).^[7]

Coca SG et al. (2017) evaluated plasma TNFR-1, TNFR-2, and KIM-1 as biomarkers of diabetic kidney disease in 190 incident DKD cases with matched controls and a 1,156-participant cohort. Higher biomarker levels were associated with renal disease progression. Adding these markers to clinical models improved prediction of renal outcomes in advanced DKD (AUC 0.68 to 0.75), supporting their prognostic value for eGFR decline.^[8]

Garg V et al. (2015) evaluated urinary Neutrophil Gelatinase-Associated Lipocalin (NGAL) and Cystatin C in 91 individuals with diabetes or pre-diabetes. Both biomarkers were significantly elevated with microalbuminuria. The urinary NGAL-to-creatinine ratio (UNCR) predicted microalbuminuria with Odds Ratio [OR] 1.070 ($p = 0.000$) in diabetes and 1.138 ($p = 0.010$) in pre-diabetes, and performed better than the urinary Cystatin C-to-creatinine ratio (UCCR), indicating their potential as early markers of nephropathy.^[9]

Zeng L et al. (2022) investigated urinary and intrarenal podocalyxin and podocin in 118 patients with biopsy-proven DKD. Intrarenal podocalyxin independently predicted dialysis-free survival (adjusted HR 1.85, 95% CI 1.21–2.82; $p = 0.005$), while urinary podocin correlated with kidney function decline ($r = 0.238$; $p = 0.01$). Urinary podocalyxin did not predict DKD progression.^[10]

Liu S et al. (2021) evaluated serum proteomic and metabolomic biomarkers in 1,513 participants across healthy, type 2 diabetes, early DKD, and advanced DKD groups. A combination of $\alpha 2$ -macroglobulin, cathepsin D, and a combination of $\alpha 2$ -macroglobulin, cathepsin D, and E-cadherin (CD324) showed potential for monitoring DKD progression, while glycerol-3-galactoside independently predicted DKD. Integrated omics improved the stability and accuracy of DKD diagnosis and prediction.^[11]

Niewczas MA et al. (2012) followed 410 patients with type 2 diabetes for 12 years, during which 59 developed end-stage renal disease (ESRD). Elevated plasma TNF receptor-1 (TNFR1) strongly predicted ESRD, with a 12-year cumulative incidence of 54% in the highest TNFR1 quartile versus 3% in the remaining quartiles ($P < 0.001$). TNFR1 remained predictive after adjustment for clinical factors, including urinary albumin excretion.^[12]

Schrauben SJ et al. (2021) evaluated plasma biomarkers in 894 patients with diabetes and chronic kidney disease (CKD) over a median follow-up of 8.7 years. Higher levels of kidney injury molecule-1 (KIM-1), tumor necrosis factor receptor-1 (TNFR-1), tumor necrosis factor receptor-2 (TNFR-2),

monocyte chemoattractant protein-1 (MCP-1), soluble urokinase plasminogen activator receptor (suPAR), and chitinase-3-like protein 1 (YKL-40) were associated with DKD progression. After adjustment, TNFR-2 showed the strongest association (adjusted HR 1.61, 95% CI 1.15–2.26), while KIM-1, TNFR-1, TNFR-2, and YKL-40 were associated with faster estimated glomerular filtration rate (eGFR) decline.^[13]

de Carvalho JA et al. (2016) evaluated urinary kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL) in 117 patients with type 2 diabetes. Urinary KIM-1 increased from 69.0±20.8 to 106.1±41.2 and 166.0±31.9 pg/mL, while NGAL increased from 29.5±8.8 to 51.7±10.9 and 71.0±9.6 ng/mL across increasing albuminuria categories (P<0.001). Both markers correlated positively with urinary albumin-to-creatinine ratio, suggesting early tubular injury in DKD.^[14]

Gohda T et al. (2020) assessed serum and urinary kidney injury molecule-1 (KIM-1) in 602 patients with type 2 diabetes and eGFR ≥30 mL/min/1.73 m². Both markers correlated positively with albumin-to-creatinine ratio and negatively with eGFR. After adjustment, both were associated with albuminuria (>30 mg/g), while only serum KIM-1 was associated with reduced eGFR (<60 mL/min/1.73 m²), suggesting stronger renal associations for serum KIM-1.^[15]

Gohda T et al. (2012) followed 628 patients with type 1 diabetes and normal renal function for 12 years. Elevated TNF receptor-1 (TNFR1) and TNF receptor-2 (TNFR2) strongly predicted early eGFR decline. Patients in the highest TNFR2 quartile had a 60% cumulative incidence of eGFR <60 mL/min/1.73 m² versus 5–19% in other quartiles, with a threefold higher risk (HR 3.0; 95% CI 1.7–5.5). TNF-α levels showed only weak or no association.^[16]

Gurung RL et al. (2025) followed 787 patients with younger-onset type 2 diabetes for 5.7 years to identify metabolic predictors of DKD progression. Lower total branched-chain amino acids (BCAAs) (OR 0.60, 95% CI 0.46–0.79), valine (OR 0.62, 95% CI 0.48–0.81), and leucine (OR 0.56, 95% CI 0.43–0.74) were independently associated with progression. Integrated metabolomic–proteomic analysis improved prediction beyond clinical factors (AUC 0.69–0.83).^[17]

Mi M et al. (2026) evaluated urinary biomarkers in 200 participants across different stages of DKD. Urinary transferrin (UTRF) and urinary immunoglobulin G (UIGG) showed strong diagnostic performance (AUC 0.926 and 0.916), while a 20-amino-acid panel achieved an AUC of 0.928. Urinary serpin family A member 1 (SERPINA1) demonstrated the highest diagnostic accuracy (AUC 0.964, 95% CI 0.936–0.990), supporting its potential as an early DKD biomarker.^[18]

Hossain MS et al. (2026) reported that urinary podocalyxin (u-PDX) increased progressively with

diabetic nephropathy severity (p < 0.001), strongly correlating with the urinary albumin-to-creatinine ratio (uACR) (r = 0.79, p < 0.001) and inversely with eGFR (r = −0.51, p < 0.001). Receiver Operating Characteristic [ROC] analysis showed excellent discrimination, with an overall cutoff of 2.92 ng/mL (AUC 0.96, 95% CI: 0.90–1.00), supporting u-PDX as a potential early biomarker of diabetic nephropathy.^[19]

Hara M et al. (2012) developed a highly sensitive Enzyme-Linked Immunosorbent Assay (ELISA) for urinary podocalyxin and found elevated levels in diabetic patients, including 53.8% at the normoalbuminuric, 64.7% at the microalbuminuric, and 66.7% at the macroalbuminuric stage. Urinary podocalyxin correlated with HbA1c and tubular injury markers, suggesting its potential as an early indicator of podocyte injury in diabetic nephropathy.^[20]

Peters KE et al. (2019) validated PromarkerD in 447 patients with type 2 diabetes. A panel of apolipoprotein A-IV (apoA4), CD5 antigen-like (CD5L), insulin-like growth factor-binding protein 3 (IGFBP3), age, high-density lipoprotein cholesterol (HDL-C), and estimated glomerular filtration rate (eGFR) predicted incident diabetic kidney disease with an AUC of 0.88 (95% CI: 0.84–0.93), 86% sensitivity, 78% specificity, and 98% negative predictive value.^[21]

Baker NL et al. (2022) assessed plasma apolipoprotein M (apoM) in 386 individuals with type 1 diabetes and found higher levels in those who progressed to macroalbuminuria (MA) or chronic kidney disease (CKD). Increased apoM was associated with greater risk of MA (RR 1.30, 95% CI: 1.01–1.66) and CKD (RR 1.69, 95% CI: 1.18–2.44), suggesting apoM as a potential early marker of diabetic nephropathy.^[22]

Chen TK et al. (2023) studied 1,135 patients with diabetes and chronic kidney disease, and found that higher urinary monocyte chemoattractant protein-1 (MCP-1) and (Chitinase-3-like protein 1 [CHI3L1]) YKL-40 levels were associated with 2.18-fold and 1.76-fold higher risks of kidney function decline, respectively. Higher neutrophil gelatinase-associated lipocalin, interleukin-18, monocyte chemoattractant protein-1, and YKL-40 levels were associated with a 10–40% increased risk of mortality over 2.2 years.^[23]

Altman J et al. (2024) studied that urinary proteomic analysis identified eight candidate proteins for diabetic kidney disease in type 1 diabetes, with AUC values of 0.959–0.995. The panel correctly classified 80% of microalbuminuric patients, supporting its potential for early DKD detection.^[24]

Li X et al. (2024) evaluated 78 propensity-matched patients with diabetes or diabetic kidney disease and found significantly elevated urinary vitamin D-binding protein (VDBP), retinol-binding protein 4 (RBP4), kidney injury molecule-1, and tumor necrosis factor receptor-2 in DKD. Their combined diagnostic performance showed an area under the curve of 0.812, sensitivity of 74.2%, and specificity

of 76.0%, supporting a multi-biomarker approach for early DKD detection.^[25]

Suwannathot A et al. (2024) prospectively evaluated 257 patients with type 2 diabetes mellitus over a median of 7 years. Urinary cystatin C, angiotensinogen, kidney injury molecule-1, and neutrophil gelatinase-associated lipocalin were higher in patients with renal progression. Their AUC ranged from 0.65–0.72, while only urinary cystatin C and kidney injury molecule-1 independently predicted the composite renal outcome of end-stage kidney disease, $\geq 40\%$ estimated glomerular filtration rate decline, or death.^[26]

Swaminathan SM et al. (2025) evaluated 145 patients with type 2 diabetes mellitus and diabetic kidney disease, of whom 38.6% were rapid progressors.

Urinary monocyte chemoattractant protein-1 showed an AUC of 0.94, with 94.1% sensitivity and 89.2% specificity, while urinary neutrophil gelatinase-associated lipocalin showed an AUC of 0.86. Their combination with urine albumin-to-creatinine ratio improved prediction (AUC 0.96).^[27]

Bano G et al. (2023) evaluated 135 participants and found that urinary angiopoietin-like protein-4 (ANGPTL-4) and kidney injury molecule-1 were associated with higher urine albumin-to-creatinine ratio and lower estimated glomerular filtration rate. Their combined diagnostic performance showed an AUC of 0.967 for microalbuminuria and 1.00 for macroalbuminuria, supporting their potential as DKD biomarkers.^[28]

Table 1: Summary of Key Findings from Studies Evaluating Emerging Biomarkers for the Early Detection and Progression of Diabetic Kidney Disease

Study	Key findings
Zürbig P et al. (2012)	A CKD peptide classifier predicted progression to macroalbuminuria up to 5 years earlier than urinary albumin (AUC 0.93 vs. 0.67), with collagen fragments as key biomarkers 3–5 years before progression.
Tofte N et al. (2020)	High-risk CKD273 scores were associated with greater progression to microalbuminuria (28% vs. 9%; HR 2.48) and impaired renal function (HR 3.50).
Coca SG et al. (2017)	Higher plasma TNFR-1, TNFR-2, and KIM-1 levels were associated with renal disease progression, improving prediction of renal outcomes in advanced DKD (AUC 0.68 to 0.75).
Garg V et al. (2015)	Urinary NGAL and Cystatin C were significantly elevated with microalbuminuria, with urinary NGAL-to-creatinine ratio predicting microalbuminuria better than urinary Cystatin C-to-creatinine ratio.
Zeng L et al. (2022)	Intrarenal podocalyxin independently predicted dialysis-free survival (adjusted HR 1.85), while urinary podocin correlated with kidney function decline ($r=0.238$).
Liu S et al. (2021)	Integrated omics identified $\alpha 2$ -macroglobulin, cathepsin D, CD324, for monitoring DKD progression and glycerol-3-galactoside as potential biomarkers for independently predicting DKD.
Niewczas MA et al. (2012)	Elevated plasma TNFR1 strongly predicted ESRD, with a 12-year cumulative incidence of 54% vs. 3% in the highest versus remaining TNFR1 quartiles.
Schrauben SJ et al. (2021)	Higher KIM-1, TNFR-1, TNFR-2, MCP-1, suPAR, and YKL-40 levels were associated with DKD progression, with TNFR-2 showing the strongest association (adjusted HR 1.61).
de Carvalho JA et al. (2016)	Urinary KIM-1 and NGAL increased progressively with albuminuria ($P<0.001$) and correlated positively with urine albumin-to-creatinine ratio.
Gohda T et al. (2020)	Serum and urinary KIM-1 correlated positively with albumin-to-creatinine ratio and negatively with estimated glomerular filtration rate.
Gohda T et al. (2012)	Elevated TNFR1 and TNFR2 strongly predicted early eGFR decline, with the highest TNFR2 quartile showing a threefold higher risk (HR 3.0).
Gurung RL et al. (2025)	Lower total BCAAs, valine, and leucine were independently associated with DKD progression, while integrated metabolomic–proteomic analysis improved prediction (AUC 0.69–0.83).
Mi M et al. (2026)	Urinary SERPINA1 showed the highest diagnostic accuracy (AUC 0.964), while UTRF, UIgG, and a 20-amino-acid panel also demonstrated strong performance.
Hossain MS et al. (2026)	Urinary podocalyxin increased with diabetic nephropathy severity and showed excellent discrimination (AUC 0.96), correlating positively with UACR and inversely with eGFR.
Hara M et al. (2012)	Urinary podocalyxin was elevated across normoalbuminuric (53.8%), microalbuminuric (64.7%), and macroalbuminuric (66.7%) stages, suggesting early podocyte injury.
Peters KE et al. (2019)	The PromarkerD panel predicted incident DKD with AUC 0.88, 86% sensitivity, 78% specificity, and 98% negative predictive value.
Baker NL et al. (2022)	Higher plasma apolipoprotein M was associated with greater risk of macroalbuminuria (RR 1.30) and chronic kidney disease (RR 1.69).
Chen TK et al. (2023)	Higher urinary MCP-1 and YKL-40 levels were associated with 2.18-fold and 1.76-fold higher risks of kidney function decline, while NGAL, IL-18, MCP-1, and YKL-40 increased mortality risk by 10–40%.
Altman J et al. (2024)	Eight urinary proteins showed excellent diagnostic performance (AUC 0.959–0.995), and the panel correctly classified 80% of microalbuminuric patients.
Li X et al. (2024)	The combination of urinary VDBP, RBP4, KIM-1, and TNFR-2 showed the highest diagnostic performance (AUC 0.812, sensitivity 74.2%, specificity 76.0%).
Suwannathot A et al. (2024)	Urinary cystatin C, angiotensinogen, KIM-1, and NGAL were higher in patients with renal progression, with AUC values of 0.65–0.72; cystatin C and KIM-1 independently predicted renal outcomes end-stage kidney disease.
Swaminathan SM et al. (2025)	Urinary MCP-1 showed an AUC of 0.94, NGAL an AUC of 0.86, and their combination with UACR improved prediction (AUC 0.96) of rapid DKD progression.
Bano G et al. (2023)	The combination of urinary ANGPTL-4 and KIM-1 showed potential as DKD biomarkers, with AUC 0.967 for microalbuminuria and 1.00 for macroalbuminuria.

CONCLUSION

Zürbig P et al. (2012) identified urinary collagen fragments as early biomarkers of diabetic nephropathy, detectable 3–5 years before macroalbuminuria, supporting urinary proteomics for early non-invasive risk prediction.^[6]

Tofte N et al. (2020) found that a high-risk CKD273 score predicted progression to microalbuminuria in normoalbuminuric type 2 diabetes over 2.5 years, while spironolactone did not prevent progression.^[7]

Coca SG et al. (2017) found that TNFR-1, TNFR-2, and KIM-1 independently predicted eGFR decline in early and advanced DKD, while their addition to clinical models improved renal outcome prediction.^[8]

Garg V et al. (2015) suggested that urinary NGAL and Cystatin C may detect early tubular injury and nephropathy in pre-diabetes and diabetes.^[9]

Zeng L et al. (2022) found that intrarenal podocalyxin predicted dialysis-free survival, while urinary podocin correlated with kidney function decline, highlighting their potential but limited routine clinical utility.^[10]

Liu S et al. (2021) showed that integrated serum proteomic and metabolomic profiles can provide stable and accurate biomarkers for early detection and diagnosis of DKD.^[11]

Niewczas MA et al. (2012) found that elevated circulating TNF receptors strongly predicted progression to ESRD in type 2 diabetes, irrespective of proteinuria.^[12]

Schrauben SJ et al. (2021) found that elevated KIM-1, TNFR-1, TNFR-2, MCP-1, suPAR, and YKL-40 were associated with DKD progression, with TNFR-2 showing the strongest association.^[13]

de Carvalho JA et al. (2016) found that urinary KIM-1 and NGAL were elevated even with normal or mildly increased albuminuria, indicating early tubular and glomerular injury in DKD.^[14]

Gohda T et al. (2020) found that serum KIM-1 was more strongly associated with renal impairment than urinary KIM-1 in type 2 diabetes.^[15]

Gohda T et al. (2012) found that circulating TNF receptor levels, but not TNF- α levels, strongly predicted early GFR decline in type 1 diabetes without proteinuria.^[16]

Gurung RL et al. (2025) found that lower plasma BCAA levels independently predicted DKD progression, while integrated multi-omics improved early risk stratification.^[17]

Mi M et al. (2026) identified urinary SERPINA1 as a promising DKD biomarker (AUC 0.964), while a 20-amino-acid panel also showed strong diagnostic performance (AUC 0.928).^[18]

Hossain MS et al. (2026) concluded that urinary podocalyxin is a promising early biomarker of diabetic nephropathy, although longitudinal studies are needed before routine clinical use.^[19]

Hara M et al. (2012) concluded that urinary podocalyxin may serve as an early biomarker of podocyte injury in diabetes.^[20]

Peters KE et al. (2019) concluded that PromarkerD accurately predicted future renal decline in people with type 2 diabetes.^[21]

Baker NL et al. (2022) concluded that early apoM alterations are associated with the development of diabetic nephropathy in type 1 diabetes.^[22]

Chen TK et al. (2023) reported that urinary tubular biomarkers, particularly monocyte chemoattractant protein-1 and chitinase-3-like protein 1 (YKL-40), were associated with kidney function decline and mortality in patients with diabetes and chronic kidney disease.^[23]

Li X et al. (2024) found that the combined urinary biomarkers vitamin D-binding protein, retinol-binding protein 4, kidney injury molecule-1, and tumor necrosis factor receptor-2 provided the highest diagnostic value for diabetic kidney disease.^[25]

Suwannathot A et al. (2024) found that urinary tubular injury biomarkers predicted chronic kidney disease progression and mortality in patients with type 2 diabetes mellitus.^[26]

Bano G et al. (2023) demonstrated the diagnostic potential of urinary angiopoietin-like protein-4 and kidney injury molecule-1 for diabetic kidney disease.^[28]

Overall, Emerging urinary, circulating, proteomic, metabolomic, and multi-biomarker panels show promising potential for the early detection and prediction of diabetic kidney disease progression, often providing information beyond conventional markers such as albuminuria and estimated glomerular filtration rate. Tubular injury, podocyte injury, inflammatory, and multi-omics biomarkers demonstrated particularly encouraging diagnostic and prognostic value. Large, multi-centre, longitudinal studies are needed to validate these biomarkers, establish standardized cut-off values, assess their added value over conventional markers, and determine their applicability in routine clinical practice.

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