Journal of Young Pharmacists, 2026; 18(2):275-285.
https://www.jyoungpharm.org

Review Article

The Molecular Signature of Diabetic Kidney Disease: A Scoping Review of Emerging Biomarker Classes

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ABSTRACT

Diabetic Kidney Disease (DKD) is the leading cause of end-stage renal disease worldwide, yet routine clinical biomarkers-albuminuria and creatinine-based estimated Glomerular Filtration Rate (eGFR)-often change only after substantial nephron loss, limiting opportunities for early intervention. This limitation is particularly important because an estimated 40-50% of people with type 2 diabetes may experience progressive renal dysfunction without albuminuria elevation (normoalbuminuric DKD), a phenotype frequently missed by conventional screening. This scoping review (PRISMA-ScR) synthesized evidence on emerging biomarkers that reflect distinct DKD pathogenic mechanisms and evaluated their diagnostic, prognostic, and implementation potential. PubMed/MEDLINE, Embase, Scopus, and Web of Science were searched for studies published from January 2005 to September 2025, yielding 37 eligible peer-reviewed studies. Evidence was organized into six biomarker domains: tubular injury (e.g., NGAL, KIM-1, L-FABP), glomerular filtration and tubular protein handling (e.g., cystatin C, low-molecular-weight proteins), inflammatory pathways (e.g., sTNFR1/2, IL-18, MCP-1), cell-cycle arrest (TIMP-2·IGFBP7), genomic/epigenetic signatures (microRNAs, exosomes), and multi-biomarker panels incorporating artificial intelligence. Across studies, novel biomarkers improved early detection (AUC ~0.75-0.90) and prognostication (hazard ratios up to ~5-6 for ESRD risk) relative to conventional measures; multi-marker approaches generally outperformed single biomarkers (AUC ~0.84-0.89 vs ~0.75-0.82). Implementation remains constrained by assay standardization, cost, and limited prospective outcomes evidence, underscoring the need for harmonized methods, large longitudinal cohorts, and biomarker-guided trials to enable precision risk stratification and earlier, targeted intervention.

Keywords: Artificial intelligence, Biomarkers, Diabetic kidney disease, Early detection, Inflammation, Multi-biomarker panel, Precision medicine, Tubular injury.

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Received: 16-12-2025;
Revised: 09-01-2026;
Accepted: 23-03-2026.

INTRODUCTION

Diabetic Kidney Disease (DKD), historically termed Diabetic Nephropathy (DN), represents a significant global public health burden and remains the leading cause of End-Stage Renal Disease (ESRD) and dialysis initiation in developed nations (Wani *et al.*, 2025). The pathogenesis of DKD involves chronic hyperglycemia-induced structural and functional damage to both glomerular and tubular renal compartments through interconnected pathways including hemodynamic stress, oxidative injury, inflammatory activation, and progressive fibrosis (Rico-Fontalvo *et al.*, 2023). Currently, the clinical paradigm for DKD diagnosis and disease monitoring relies predominantly on two "conventional" biomarkers: albuminuria and estimated Glomerular Filtration Rate (eGFR) derived from serum creatinine concentration (Wani *et al.*, 2025). However, these traditional markers possess significant limitations-specifically, they typically change only after substantial nephron loss has already occurred, resulting in delayed disease detection and missed opportunities for early renoprotective interventions (Wani *et al.*, 2025).

A critical limitation of albuminuria-centric DKD definition has emerged from epidemiological and pathological observations:

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DOI: 10.5530/jyp.20260318

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a substantial proportion of patients with diabetes develops progressive eGFR decline in the absence of increased urinary albumin excretion, a phenotype termed Normoalbuminuric Diabetic Kidney Disease (NADKD) (Shetty *et al.*, 2025). Contemporary evidence demonstrates that this subgroup may comprise up to approximately 40-50% of individuals with type 2 diabetes presenting with renal functional impairment (Olatunde *et al.*, 2025). Furthermore, kidney biopsy studies reveal that both albuminuric and normoalbuminuric phenotypes exhibit advanced histopathological lesions including glomerulosclerosis, arteriolar hyalinosis, and tubulointerstitial fibrosis, underscoring that albuminuria alone fails to capture the spectrum of renal pathology and cannot serve as a reliable early detection marker (Olatunde *et al.*, 2025). This discordance between functional and histological disease demonstrates the urgent need for more sensitive, pathophysiology-based biomarkers that reflect early structural kidney damage independent of proteinuria status (Fiseha, 2020).

Over the past two decades (2005-2025), intensive biomedical research has identified numerous novel biomarkers reflecting distinct pathogenic mechanisms operative in DKD that facilitate earlier disease detection, enhanced risk stratification, and improved prognostication (Wani *et al.*, 2025). Foremost among these are tubular injury markers. Accumulating evidence indicates that renal tubular epithelial cell damage often precedes clinically apparent glomerular dysfunction in the diabetic kidney (Fiseha, 2020). Consequently, biomarkers released by injured tubular cells have attracted substantial investigative attention as early indicators of subclinical kidney injury. Established tubular biomarkers include Neutrophil Gelatinase-Associated Lipocalin (NGAL), Kidney Injury Molecule-1 (KIM-1), and liver-type Fatty Acid-Binding Protein (L-FABP), among others (Zeng *et al.*, 2017). The present scoping review therefore systematically synthesizes current evidence on emerging biomarker classes for DKD, describes their pathophysiological relevance, summarizes key validation studies with attention to diagnostic and prognostic performance metrics, and discusses implications for advancing precision diagnostics and targeted interventions in diabetic kidney disease.

METHODOLOGY

This scoping review was conducted in accordance with the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) guidelines to ensure transparent and reproducible reporting. A comprehensive literature search was performed in PubMed/MEDLINE, Embase, Scopus, and Web of Science to identify studies published between January 2005 and September 2025 that evaluated biomarkers relevant to the early detection, monitoring, or prognosis of diabetic nephropathy/Diabetic Kidney Disease (DKD).

Search Strategy and Eligibility Criteria

The search strategy combined controlled vocabulary (e.g., MeSH terms where applicable) and free-text keywords related to DKD and biomarkers, including terms such as "diabetic nephropathy," "diabetic kidney disease," "biomarkers," "NGAL," "KIM-1," "L-FABP," "TNFR-1/2," "microRNA," "exosomes," and "cell-free DNA." Boolean operators (AND/OR) were applied to optimize retrieval, and the reference lists of eligible papers were manually screened to identify additional relevant studies.

Studies were included if they: (i) involved human participants with type 1 or type 2 diabetes; (ii) evaluated one or more DKD-relevant biomarkers; and (iii) reported diagnostic or prognostic outcomes (e.g., albuminuria status, eGFR decline, DKD progression). Studies were excluded if they were animal-only research, case reports, conference abstracts without sufficient data, narrative reviews, non-English publications, or not directly related to biomarker evaluation in DKD.

Study Selection and Data Extraction

After duplicate removal, titles and abstracts were screened, followed by full-text assessment of potentially eligible records. Two reviewers independently screened studies and extracted data; any disagreements were resolved through consensus discussion. Extracted data included study design, participant characteristics, biomarker type and sample source (e.g., urine, blood), comparator measures (where available), and reported clinical endpoints.

Quality Appraisal and Synthesis Approach

Study quality was assessed using the Newcastle-Ottawa Scale for observational studies and QUADAS-2 where appropriate for diagnostic accuracy studies. Given heterogeneity across study designs, populations, assays, and reported outcomes, findings were synthesized narratively and organized into six thematic biomarker domains: tubular injury, glomerular dysfunction/filtration barrier markers, inflammatory and oxidative stress biomarkers, cell-cycle arrest markers, genomic/epigenetic biomarkers, and exosomal/omics-derived signatures.

The study identification and selection process is summarized in the PRISMA-ScR flow diagram (Figure 1).

RESULTS

Across the 37 included studies, evidence clustered into six biomarker domains. To keep the presentation cohesive and mechanism-led, we summarize tubular injury markers first (early epithelial stress), then filtration-barrier and tubular protein-handling markers, followed by inflammatory pathways, cell-cycle arrest, and finally genomic/epigenetic and multi-marker/AI approaches.

Tubular injury biomarkers were the most frequently evaluated early-detection candidates; Table 1 synthesizes representative studies and key performance metrics for this domain.

Glomerular Filtration and "Filtration Barrier" Markers

After early tubular stress, glomerular and filtration-barrier dysfunction becomes clinically evident. Glomerular damage in diabetic nephropathy compromises filtration barrier integrity, resulting in proteinuria and declining glomerular filtration rate (Olatunde *et al.*, 2025). While serum creatinine-derived eGFR remains the clinical standard, alternative markers offer superior early detection. Key filtration-function biomarkers and supporting studies are synthesized in Table 2.

Inflammatory and Oxidative Stress Biomarkers

Evidence on inflammatory and oxidative stress biomarkers is summarized in Table 3.

Inflammation emerges as a major pathogenic driver in diabetic kidney injury, triggered by chronic hyperglycemia-induced cytokine release and fibrogenic signaling (Shetty *et al.*, 2025). Soluble TNF receptors (sTNFR1 and sTNFR2) represent exceptionally powerful prognostic biomarkers, with elevated levels predicting rapid glomerular filtration rate decline, renal failure, and mortality (Rico-Fontalvo *et al.*, 2023). Baseline TNFR1/TNFR2 outperform albuminuria for predicting 10-year end-stage renal disease risk. Interleukin-18, overexpressed in diabetic tubular epithelium, predicts microalbuminuria onset, particularly when combined with neutrophil gelatinase-associated lipocalin (Mahapatra *et al.*, 2025). Additional inflammatory mediators including monocyte chemoattractant protein-1, osteopontin, calprotectin, and YKL-40 correlate with disease severity and progression (Shetty *et al.*, 2025). Oxidative stress markers including 8-hydroxy-2'-deoxyguanosine reflect ongoing renal injury. Collectively, inflammatory biomarkers demonstrate exceptional value for identifying high-risk patients warranting intensive renoprotective interventions. The key studies and biomarker performance metrics discussed in this section are summarized in Table 3.

Cell Cycle Arrest Markers in Diabetic Kidney Disease

The Cell Cycle Arrest Biomarkers (TIMP-2 · IGFBP7), in acute kidney injury research, the detection of cell cycle arrest in stressed renal tubular cells has emerged as a novel biomarker strategy. Two proteins-Tissue Inhibitor of Metalloproteinases-2 (TIMP-2) and Insulin-like Growth Factor Binding Protein-7 (IGFBP7)-are released by cells entering G1 cell cycle arrest, a protective mechanism proximal tubule cells employ to avoid division under sublethal stress (Vijayan *et al.*, 2023). The combination of these biomarkers ([TIMP-2]·[IGFBP7]) forms the basis of the FDA-approved NephroCheck® test for acute kidney injury risk prediction within 12-24 hr. While initially developed for acute kidney injury, growing interest exists regarding the relevance of these markers for detecting ongoing tubular stress or subclinical acute kidney injury episodes superimposed on chronic diabetic kidney disease.

Diabetic patients-particularly those with advanced diabetic kidney disease-face elevated risk for acute kidney injury episodes, which accelerate disease progression. TIMP-2 and IGFBP7 may flag these acute-on-chronic renal insults. Surgical patient studies demonstrated that these markers predict acute kidney injury development and 30-day mortality, with diabetes being a major risk factor in such contexts (Olsson *et al.*, 2025).

Renal biopsy studies revealed that TIMP-2 and IGFBP7 expression is upregulated in diseased kidneys, including diabetic nephropathy, compared to healthy tissue. Specifically, kidney biopsy analysis reported significantly higher TIMP-2 and IGFBP7 in chronic kidney disease patients with diabetic nephropathy than in healthy controls, particularly localized to distal tubular cells, indicating chronic cell-cycle arrest signaling in diseased kidneys.

Current evidence on TIMP-2·IGFBP7 (NephroCheck) in DKD is summarized in Table 4.

Currently, no large longitudinal diabetic cohort study has established [TIMP-2]. [IGFBP7] as a diabetic kidney disease progression predictor. However, elevated levels reflecting ongoing tubular stress may indicate faster glomerular filtration rate decline. In summary, TIMP-2·IGFBP7 represents a validated acute kidney injury risk biomarker with potential future chronic diabetic kidney disease applications, functioning as a "renal stress test" detecting tubular cell stress before cellular death. If diabetic patients chronically express elevated markers, this may indicate persistent renal stress requiring aggressive intervention including glycemic control and renin-angiotensin-aldosterone system inhibition. Further research defining TIMP-2·IGFBP7's role in chronic diabetic nephropathy remains essential.

TIMP-2 and IGFBP7 represent emerging biomarkers at the intersection of acute and chronic kidney injury. As part of a scoping review, they are included for completeness given the user's interest, but they are not yet established in routine DN management. Their main message is the presence of tubular cell stress and arrest, which is certainly a feature of progressive DKD.

Genomic and Epigenetic Biomarkers (microRNAs, Exosomal Markers, etc.,)

Advances in genomics and omics technologies have opened new avenues for identifying non-traditional biomarkers in biofluids. In DKD, microRNAs (miRNAs), long non-coding RNAs, circulating DNA, and urinary extracellular vesicles (exosomes) may act as stable molecular readouts of transcriptional and epigenetic remodeling.

Urinary MicroRNAs represent approximately 20-22 nucleotide RNA molecules that regulate gene expression post-transcriptionally. Many miRNAs are dysregulated in diabetic kidneys, influencing fibrosis, inflammation, and metabolic pathways (Taneska *et al.*, 2025). Critically, miRNAs are stable in urine-often encapsulated in exosomes-enabling noninvasive measurement. Numerous studies identified specific miRNA panels associated with diabetic kidney disease. Pro-fibrotic miRNAs including miR-21, miR-192, and miR-216a are upregulated in diabetic kidneys and urine, whereas protective miRNAs like miR-29, miR-200, and miR-126 are downregulated (Taneska *et al.*, 2025). Meta-analytic data found certain circulating miRNAs (miR-21, miR-29a) demonstrate diagnostic accuracy with AUC of approximately 0.8-0.9 for diabetic nephropathy. Specifically, miR-21 promotes renal fibrosis by targeting antifibrotic pathways and is consistently elevated in plasma and urine of diabetic kidney disease patients. Inhibiting miR-21 in animal models attenuates disease progression, establishing it as both a biomarker and therapeutic target. MiR-192, induced by transforming growth factor-beta, drives glomerular collagen production; high urinary miR-192 correlates with albuminuria severity. Conversely, miR-126-3p and miR-29a, which protect endothelium and prevent fibrosis respectively, are decreased in diabetic kidney disease, with low levels correlating with worse outcomes. Because individual miRNA levels vary substantially, investigators now profile multiple miRNA panels to enhance diagnostic accuracy, with combined urine miRNA panels achieving >90% sensitivity for early diabetic nephropathy detection (Taneska *et al.*, 2025).

Urinary Exosomes and Cargo are nano-sized vesicles shed by cells into urine, containing proteins, messenger RNAs, and miRNAs representative of their cell origin. Kidney tubule cells actively secrete exosomes, making urine a "liquid biopsy" of kidney tissue. In diabetic kidney disease, urinary exosomes carry disease signals distinguishing diabetic from non-diabetic renal disease. Exosomal miRNA profiles differ markedly in diabetic nephropathy; for example, miR-145-5p and miR-130a in urinary exosomes were upregulated and induced podocyte apoptosis through RhoA pathway activation (Olatunde *et al.*, 2025). Urinary exosomal miR-136-5p was significantly higher in diabetic kidney disease patients versus diabetics without nephropathy. These findings suggest exosomal markers serve as early disease indicators. A 2021 review affirmed "urinary exosomes have emerged as promising biomarkers for early detection of diabetic nephropathy," given their content mirrors renal pathology. Ongoing efforts catalog exosomal proteomes and RNA signatures in large patient cohorts to identify reproducible diabetic nephropathy markers. Technical challenges including isolating pure exosomes requiring analytical standardization represent current limitations in this cutting-edge biomarker domain.

The key studies and biomarker performance metrics discussed in this section are summarized in Table 5.

Emerging Multi-Biomarker Panels and AI Integration

Given the multitude of promising biomarkers, recent research has shifted toward combining multiple markers to enhance diagnostic and prognostic performance. The rationale is that integrated panels capture complementary pathophysiological processes,

Table 1: Selected Studies of Tubular Injury Biomarkers in Diabetic Kidney Disease (2005-2025)

Study (Year)	Population	Biomarker(s)	Key Findings
Zeng *et al.*, 2017	146 T2DM patients (various albuminuria stages)+controls	Urine NGAL, CLU, Cystatin C	NGAL and cystatin C elevated in normoalbuminuric DKD (AUC 0.82 for DKD diagnosis); clusterin elevated only with microalbuminuria
Fiorentino *et al.*, 2018	190 T2D (ACCORD)+1,156 (VA NEPHRON-D)	Plasma KIM-1, TNFR1, TNFR2	KIM-1 and TNFR1/2 ~2× higher in advanced DKD; adding biomarkers to clinical models improved AUC from 0.68 to 0.75
Nielsen *et al.*, 2010	1,549 type 1 diabetics (~6-year follow-up)	Urine L-FABP	Urinary L-FABP elevated in normoal buminuria (0.075 vs 0.014 µg/µmol Cr); independent predictor of DKD progression (HR ~1.4, $p<0.01$)
Satirapoj, 2018	Literature Review (DN cohorts)	NGAL, NAG, KIM-1	Tubular markers rise before glomerular injury; combined assessment improves early DKD diagnosis
Bolignano *et al.*, 2009	72 T2DM+50 controls	Urine NGAL	Urinary NGAL elevated in micro/macroalbuminuric diabetics ($p<0.001$); serves as early tubular damage marker
Nauta *et al.*, 2011	345 T2DM (no baseline proteinuria)	Urine α1MG, β2MG	Low-molecular-weight proteins associated with microalbuminuria development; highest quartile showed higher 4-year progression risk

(Abbreviations: T2D=Type 2 Diabetes; T1D=Type 1 Diabetes; DKD=Diabetic Kidney Disease; NGAL=Neutrophil Gelatinase-Associated Lipocalin; CLU=Clusterin; CysC=Cystatin C; KIM-1=Kidney Injury Molecule-1; TNFR1/2=Tumor Necrosis Factor Receptor 1/2; L-FABP=Liver-Type Fatty Acid-Binding Protein; NAG=N-Acetyl-Glucosaminidase; AER=Albumin Excretion rate; MG=Microglobulin.)

Table 2: Studies on Filtration Function Biomarkers in DN.

Study (Year)	Population	Biomarker(s)	Main Outcomes
Perkins *et al.*, 2003	139 Type 1 Diabetics (Normoalbuminuric Baseline)	Serum Cystatin C vs Creatinine	Over ~8 years, cystatin C detected GFR decline earlier than creatinine; missed only 30% of cases at 50% GFR loss compared to creatinine. More sensitive early GFR marker in incipient DN.
Jerums *et al.*, 2010	662 Type 2 Diabetics with Normoalbuminuria (5-year follow-up)	Urine β2MG, A1M, Albumin	Patients developing microalbuminuria had significantly higher baseline urinary β2MG and α1MG.>80% specificity for albuminuria conversion. Combining albumin with low-molecular-weight proteins improves early risk stratification.
Frydland M *et al.*, Shock. 2018	216 Type 1 Diabetics (Mixed Albuminuria)	Urine IgG & IgM	Urinary IgG and IgM elevated in DN, correlating with albuminuria and GFR decline. High IgM associated with faster ESRD progression. Immunoglobulin markers reflect severe glomerular leak.
Yang *et al.*, 2022	120 Type 2 Diabetics (early DKD)	Serum vs Urine Cystatin C	Serum cystatin C superior to creatinine for early eGFR reduction detection. Urinary cystatin significantly higher in microalbuminuria, indicating tubular impairment. Both compartments valuable for early DKD diagnosis.
Huang YL, *et al.*, 2024	92 Type 2 Diabetics (CKD stage 0-3)	Urine RBP4, NGAL, Albumin	Urinary RBP4 elevated in early albuminuria; correlated with tubular injury marker NGAL. RBP4+NGAL combination improved microalbuminuria detection (AUC ~0.88).

(Abbreviations: A1M=α1microglobulin; β2MG=β2microglobulin; RBP4=Retinol-Binding Protein 4.)

such as tubular injury, inflammation, and impaired glomerular filtration, providing a more comprehensive assessment of disease risk than any single biomarker alone (Shetty *et al.*, 2025).

Omics-based and machine-learning approaches further advance this strategy by enabling unbiased identification of optimal biomarker combinations. Proteomics studies have identified multi-protein classifiers incorporating collagen and clusterin fragments that predict diabetic kidney disease progression more accurately than albuminuria alone (Peña *et al.*, 2016). Similarly, metabolomic signatures involving amino acids and acyl-carnitines have been associated with early glomerular filtration rate decline, underscoring the potential of systems-level biomarker discovery.

Figure 2 illustrates a conceptual framework for multi-biomarker integration in diabetic kidney disease, highlighting how biomarkers reflecting tubular injury, inflammation, and glomerular dysfunction can be combined with clinical variables using artificial intelligence algorithms to generate actionable risk stratification. This integrated approach supports the transition toward precision medicine, enabling earlier intervention and more personalized management strategies in diabetic kidney disease.

DISCUSSION

KidneyIntelX™: Artificial Intelligence-Based Risk Stratification represents a landmark application of biomarker integration. Investigators developed KidneyIntelX, a machine learning-based prognostic test integrating three plasma biomarkers (TNFR1, TNFR2, and KIM-1) with patient clinical data including age, eGFR, hemoglobin A1c, and blood pressure in an artificial intelligence algorithm to predict rapid diabetic kidney disease progression in patients with stage 1-3 chronic kidney disease (Nadkarni *et al.*, 2023). In June 2023, KidneyIntelX.dkd received U.S. FDA De Novo marketing authorization as an *in vitro* prognostic test to aid assessment of risk for progressive kidney function decline in adults with type 2 diabetes and early-stage CKD. Validation studies successfully stratified patients into low, medium, and high risk categories for 5-year progression, substantially improving upon standard risk models. One study of approximately 1,100 patients demonstrated that the KidneyIntelX high-risk group achieved a positive predictive value of 62% for progressive decline, significantly superior to clinical factors or Kidney Disease: Improving Global Outcomes risk stratification alone (Nadkarni *et al.*, 2023). This test exemplifies artificial intelligence integration of biomarkers: it combines inflammatory markers (TNFR1/TNFR2) and tubular injury signals (KIM-1) that together powerfully indicate aggressive diabetic kidney disease. This multi-marker approach guides clinical decision-making-high-risk patients warrant early

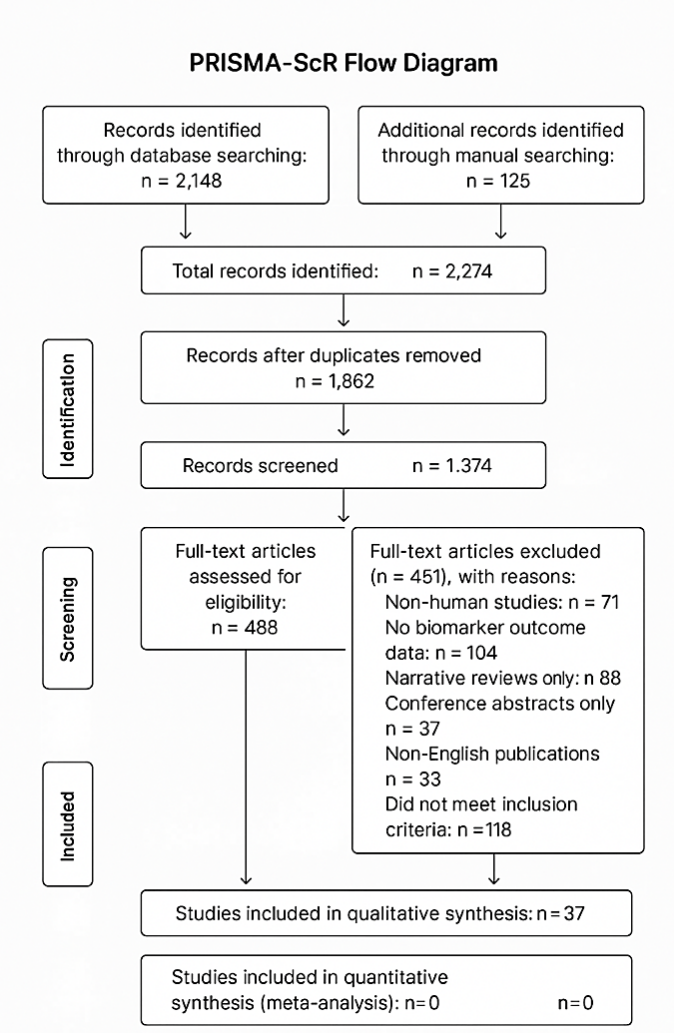

Figure 1: PRISMA-ScR flow diagram of study selection.

specialist referral or intensive therapy, whereas lower-risk patients may be managed in primary care settings (Shetty *et al.*, 2025).

Multi-Marker Panels for Early Detection extend beyond prognostication. Evaluated a panel combining urinary N-terminal osteopontin, ANGPTL4, and KIM-1, finding improved prediction of microalbuminuria conversion in diabetic patients. Similarly, combined assessment of neutrophil gelatinase-associated lipocalin, L-FABP, and cystatin C detects diabetic kidney disease earlier than albumin alone, with general findings indicating multi-marker models outperform single markers in sensitivity and specificity

This scoping review synthesizes evidence across multiple biomarker domains and reinforces a central message: Diabetic Kidney Disease (DKD) is biologically heterogeneous, and conventional clinical markers-albuminuria and creatinine-based eGFR-often detect disease only after substantial structural injury has occurred. Contemporary work emphasizes that delayed detection is especially problematic for normoalbuminuric phenotypes, where progressive eGFR decline may develop without a parallel rise in albumin excretion, limiting the sensitivity of albuminuria-centric screening approaches (Shetty *et al.*, 2025; Wani *et al.*, 2025). This misalignment between clinical staging and underlying pathology supports the need for biomarkers that reflect early cellular injury, inflammatory activation, and fibrotic remodeling rather than late functional consequences.

A prominent theme in the mapped literature is the early involvement of the tubulointerstitial compartment. Tubular injury biomarkers-including NGAL, KIM-1, and L-FABP-are frequently elevated in diabetic individuals with preserved or only mildly impaired conventional measures, suggesting that tubular epithelial stress may occur early and may contribute materially to downstream decline (Fiseha and Tamir, 2020; Zeng *et al.*, 2017). Longitudinal evidence further supports clinical relevance: urinary L-FABP has been associated with progression risk across albuminuria strata, indicating that tubular injury signals can predict worsening renal outcomes even when albuminuria alone is insufficient to capture trajectory (Nielsen *et al.*, 2010). Practically, these observations argue for risk models that incorporate tubular markers to identify patients with subclinical kidney injury who might otherwise be classified as low risk using standard markers.

Inflammatory biomarkers emerge as especially strong prognostic indicators. Soluble TNF receptors (TNFR1/TNFR2) show consistent associations with accelerated eGFR decline and end-stage renal disease, often independent of albuminuria and baseline renal function, implying that they capture upstream inflammatory and endothelial pathways linked to irreversible nephron loss (Panduru *et al.*, 2015; Rico-Fontalvo *et al.*, 2023). Complementing these, urine inflammatory mediators such as MCP-1 and IL-6 appear higher in rapid progressors, supporting the concept that intrarenal inflammatory activity is measurable noninvasively and can stratify progression risk (Fujita *et al.*, 2020). Together, these findings position inflammatory biomarkers as candidates not only for prognostication but also for enriching high-risk cohorts in future interventional studies (Shetty *et al.*, 2025).

The review also identifies a translational bridge between acute and chronic injury biology. Cell-cycle arrest biomarkers (TIMP-2·IGFBP7) are well established in acute kidney injury prediction and have been proposed as indicators of tubular stress that may occur in high-risk diabetic contexts (Bihorac *et al.*, 2014; Vijayan *et al.*, 2023). Evidence from kidney tissue studies suggests upregulation of these stress pathways in chronic kidney disease, including DKD, but DKD-specific longitudinal validation remains limited, warranting cautious interpretation at present (Fiorentino *et al.*, 2018).

Finally, the strongest near-term implementation pathway appears to be multi-marker integration (Table 6). Combining inflammatory (TNFR1/2) and tubular injury (KIM-1) signals improves discrimination beyond clinical models alone, and

Table 3: Inflammatory Biomarkers and DN Progression: Key Evidence

Study (Year)	Population	Biomarker(s)	Key Results
Jacobson AM, *et al.*, 2021	198 Type 1 Diabetics (DCCT/EDIC cohort)	Plasma sTNFR1, sTNFR2, IL-6, sE-selectin	Baseline TNFR1/2 and IL-6 significantly higher in those developing microalbuminuria. sTNFR1 and sTNFR2 strongest predictors of microalbuminuria onset (HR ~3 per SD). High TNFR predicted greater HbA1c-related GFR loss.
Panduru *et al.*, 2015	349 Type 1 Diabetics with proteinuria (FinnDiane)	Plasma TNFR2	TNFR2 main determinant of eGFR decline in established DN. Highest TNFR2 levels associated with markedly faster annual GFR loss, especially with poor glycemic control. Predictive after adjusting for baseline GFR and A1c.
Saraheimo *et al.*, 2011	158 Type 1 Diabetics (Joslin cohort)	Plasma TNFR1, TNFR2	First showed TNFR1/2 as strong ESRD predictors. Over 12 years: ~50% in top tertile progressed to ESRD vs <10% lowest tertile. HR ~5-6 for ESRD (independent of albuminuria).
Fujita *et al.*, 2020	82 Type 2 Diabetics (biopsy-proven DKD)	Urine MCP-1, IL-6, TNF-α	Urinary MCP-1 and IL-6 significantly higher in rapid progressors (≥5 mL/min/yr GFR loss) vs slow progressors. Urine inflammatory cytokines stratify rapid progression risk.
Dalla Vestra *et al.*, 2005	35 Type 2 Diabetics+30 controls	Renal biopsy TNF-α, TGF-β, IL-18	Microalbuminuric patients showed higher glomerular TNF-α and IL-18 expression on biopsy. These mediators localized to glomeruli and tubules. Local TNF/IL-18 upregulation initiates nephropathy.
Panchapakesan *et al.*, 2013	Review (*in vitro* and animal models)	Nrf2, NF-κB pathways	Hyperglycemia triggers NF-κB, promoting IL-6, TNF-α, MCP-1 production. Oxidative stress pathway (Nrf2) dysregulated. Advocates multi-marker panels capturing inflammation and oxidative stress.

(Abbreviations: sTNFR=Soluble TNF Receptor; IL=Interleukin; MCP-1=Monocyte Chemoattractant Protein-1; TGF-β=Transforming Growth Factor beta; NF-κB=Nuclear Factor Kappa B; Nrf2=Nuclear Factor Erythroid 2-Related Factor 2.)

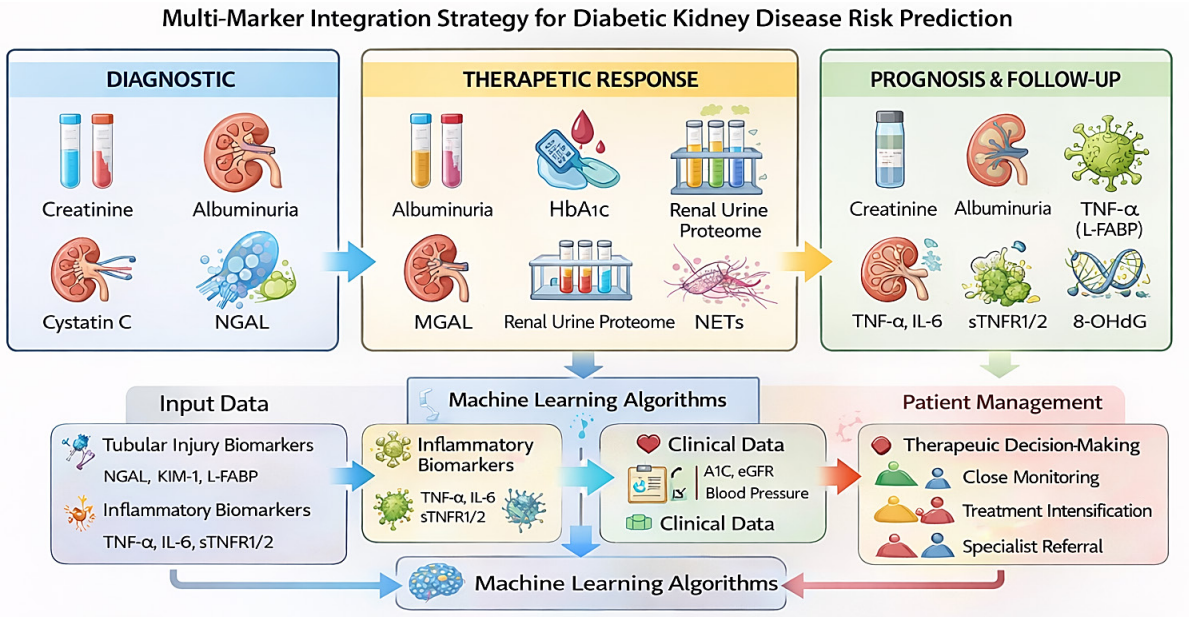

Figure 2: Multi-biomarker integration strategy for diabetic kidney disease risk prediction.

Schematic representation illustrating how tubular injury biomarkers (e.g., NGAL, KIM-1), inflammatory markers (e.g., TNFR1/2), and glomerular filtration markers (e.g., cystatin C) are integrated with clinical variables using artificial intelligence-based algorithms to generate risk stratification scores across the diabetic kidney disease care continuum.

Table 4: TIMP-2 · IGFBP7 (NephroCheck) and DKD - Current Insights.

Source/Study	Context	Findings
Bihorac *et al.*, 2014 (Lancet, Sapphire)	Critical care AKI trial (≈20% with diabetes)	Identified urinary [TIMP-2]·[IGFBP7] as the best-performing biomarkers for imminent AKI. Patients with highest NephroCheck scores had ~7-fold higher AKI risk, indicating cell-cycle arrest markers detect subclinical tubular injury before creatinine rises.
Wetz *et al.*, 2015 (Kidney Int)	Meta-analysis of AKI biomarkers in surgical patients	Diabetes associated with higher baseline [TIMP-2]·[IGFBP7] and higher AKI incidence, suggesting the diabetic milieu primes kidneys to express these stress markers. Calls for studies in stable DKD to determine chronic elevation vs non-diabetics.
Fiorentino *et al.*, 2018 (Kidney Int Rep)	Biopsy-based study of DKD and other CKDs	TIMP-2 and IGFBP7 overexpressed in CKD tissue vs normal kidneys, with diabetic kidneys showing particularly high TIMP-2 in distal tubules and IGFBP7 in multiple tubular segments. Indicates chronic cell-cycle arrest signaling in DKD.
Heller & Fioretto, 2017 (Diabetes Care)	Commentary on AKI in diabetes	Emphasizes diabetes as a "bona fide" AKI risk factor. Proposes integrating AKI biomarkers such as NephroCheck into diabetes care (hospitalized or high-risk DKD patients), while noting that outpatient utility remains unproven.
Ongoing trials (2023-2025)	High-risk diabetic cohorts (e.g., contrast procedures, major surgery)	Early-phase studies are measuring [TIMP-2]·[IGFBP7] to assess prediction of AKI and subsequent CKD worsening in diabetics. No large prospective DKD-specific outcomes published yet.

(Abbreviations: AKI=Acute Kidney Injury; ICU=Intensive Care Unit).

Table 5: Genomic/Epigenetic Biomarkers in DN: Recent Findings

Study	Biomarker	Findings in DN
Kato *et al.*, 2007	Renal miRNA expression (mouse & human)	Identified a signature of 7 miRNAs consistently dysregulated in diabetic kidneys. Notably, miR-21, miR-200b/c, miR-216a up, and miR-29a/b, miR-192 down in DN glomeruli. These changes drove TGF-β signaling and collagen deposition. Inhibition of miR-21 in diabetic mice reduced albuminuria.
Argyropoulos *et al.*, 2015 (CJASN)	Urinary miRNA (30 DKD pts)	Urinary miR-21 and miR-216a levels were elevated in DKD patients and correlated with degree of albuminuria. miR-21 was highest in macroalbuminuric patients, supporting it as a marker of progressive fibrosis. Urine miR-29a was low in those with fibrosis.
Barutta *et al.*, 2013 (JASN)	Urine exosomal miRNAs (T1D)	In type 1 diabetics, urinary exosomal miR-130a and miR-145 were significantly higher in patients with microalbuminuria compared to those without. These miRNAs targeted pro-survival pathways in podocytes. Suggests exosomal miR changes precede overt nephropathy.
Zubiri *et al.*, 2014 (J Proteome Res)	Urine exosome proteomics	Proteomic analysis of urinary exosomes found increase in proteins like ACE2, transferrin, and decrease in podocin in DN vs controls. A panel of 10 exosomal proteins could discriminate DN with >90% accuracy. These proteins reflect glomerular and tubular damage components in DN.
Papale *et al.*, 2014 (J Am Soc Nephrol)	Urine DNA methylation markers	Tested urinary sediment DNA for differential methylation. Found that hypomethylation of the UNC13B gene promoter in urine DNA was associated with DKD progression in T1D patients. This epigenetic mark in urine could predict whose nephropathy would worsen.
Morikawa *et al.*, 2021 (Sci Rep)	Plasma cfDNA (mitochondrial)	Plasma mitochondrial DNA (mtDNA) levels were elevated in DKD patients vs diabetic controls. High mtDNA correlated with tubulointerstitial injury score on biopsy. mtDNA is a damage-associated molecular pattern, indicating tissue injury. Could be a novel plasma biomarker for active kidney damage in DN.

(miR=microRNA; cfDNA=Cell-Free DNA.)

Table 6: Overview of biomarker domains, sample sources, and typical performance metrics reported across included studies.

Biomarker domain	Typical sample	What it captures (mechanism)	Common endpoints reported	Typical performance signals (range)	Study
Tubular injury (NGAL, KIM-1, L-FABP)	Urine / plasma	Early tubular epithelial stress and injury	DKD detection in normoalbuminuria; eGFR slope; albuminuria conversion	AUC ~0.75–0.85; HR ~1.3–1.8 (progression)	Zeng *et al.*, 2017; Nielsen *et al.*, 2010; Satirapoj, 2018
Filtration / tubular protein handling (cystatin C, β2MG, α1MG, RBP4)	Serum and urine	Early GFR change and proximal tubular reabsorption defects	Early eGFR decline; microalbuminuria conversion	Improves sensitivity vs creatinine; AUC up to ~0.85–0.88 (combined panels)	Perkins *et al.*, 2003; Jerums *et al.*, 2010; Yang *et al.*, 2022
Inflammation (sTNFR1/2, IL-18, MCP-1, IL-6)	Plasma / urine	Systemic and intrarenal inflammatory activation linked to nephron loss	Rapid eGFR decline; ESRD; mortality	HR up to ~5–6 for ESRD; additive to albuminuria	Panduru *et al.*, 2015; Saraheimo *et al.*, 2011; Fujita *et al.*, 2020
Cell-cycle arrest (TIMP-2·IGFBP7)	Urine	Tubular stress and G1 arrest (acute-on-chronic injury biology)	AKI risk; exploratory DKD progression signals	Validated for AKI prediction; DKD longitudinal evidence limited	Bihorac *et al.*, 2014; Fiorentino *et al.*, 2018; Vijayan *et al.*, 2023
Genomic/epigenetic (miRNAs, exosomes, cfDNA)	Urine (exosomes), plasma	Transcriptional/ epigenetic remodeling; cell-to-cell signaling cargo	DKD detection; fibrosis severity; progression risk	AUC ~0.80–0.90 in some panels; requires harmonized methods and validation	Kato *et al.*, 2007; Argyropoulos *et al.*, 2015; Barutta *et al.*, 2013; Zubiri *et al.*, 2014
Multi-marker / AI panels (e.g., TNFR1/2 + KIM-1 + clinical features)	Plasma + EHR variables	Integrated risk modeling across pathways	5-year progressive decline risk stratification	Often outperforms single markers; AUC ~0.84–0.89	Nadkarni *et al.*, 2023

AI-enabled strategies (e.g., KidneyIntelX.dkd) operationalize this principle by integrating biomarkers with clinical variables to generate actionable risk categories. However, translation to routine care depends on practical laboratory and health-system constraints: assay harmonization (reference materials, inter-laboratory reproducibility, and lot-to-lot stability), standardized pre-analytics (collection timing, storage, freeze-thaw cycles), and consistent reporting units and normalization strategies (especially for urine analytes). For emerging omics assays, additional challenges include exosome isolation protocols, RNA extraction efficiency, and batch effects. In parallel, prospective studies are needed to show that biomarker-guided stratification changes management and improves patient-centered outcomes rather than only improving prediction metrics (Wani *et al.*, 2025). Over the longer term, microRNA and exosome-based signatures may enable molecular phenotyping of DKD, but technical and longitudinal validation challenges must be addressed before clinical translation (Taneska *et al.*, 2025).

Limitations and implications for future studies

Several limitations of the mapped evidence base should temper interpretation. First, study populations were heterogeneous (type 1 vs type 2 diabetes, varying baseline eGFR/albuminuria strata, and variable comorbidity burden), which limits direct comparability of effect sizes across cohorts. Second, biomarker assays and pre-analytical handling differed widely (sample matrix, timing, normalization to urine creatinine, and platform-specific calibration), contributing to between-study variability and complicating threshold definition for clinical use. Third, many studies were cross-sectional or used surrogate endpoints (albuminuria conversion, short-term eGFR slope) rather than hard outcomes, and few evaluated whether biomarker-guided risk stratification changes management or improves kidney endpoints. Finally, AI-enabled models may be vulnerable to overfitting, spectrum bias, and limited transportability if trained in narrowly defined health-system datasets; transparent reporting and external validation in diverse settings are essential.

CONCLUSION

Over two decades, biomarker research has transformed diabetic kidney disease diagnostics. Traditional markers-albuminuria and creatinine-prove insufficient for early detection. Novel biomarkers spanning tubular injury (NGAL, KIM-1, L-FABP), glomerular dysfunction (cystatin C), inflammation (TNFR1/2, IL-18), and fibrosis (microRNAs) enable earlier diagnosis and better prognostication. Integrated multi-marker panels, exemplified by artificial intelligence-driven tools like KidneyIntelX, demonstrate superior predictive performance. Despite regulatory and standardization challenges limiting current clinical adoption, the field is advancing toward personalized risk profiling and precision medicine. Future strategies combining biomarker-guided diagnostics with emerging therapeutics including sodium-glucose cotransporter-2 inhibitors and fibrosis antagonists will revolutionize diabetic kidney disease management, shifting from reactive treatment to proactive early intervention and improved renal outcomes.

ABBREVIATIONS

DKD: Diabetic Kidney Disease; **DN:** Diabetic Nephropathy; **ESRD:** End-Stage Renal Disease; **CKD:** Chronic Kidney Disease; **AKI:** Acute Kidney Injury; **eGFR:** Estimated Glomerular Filtration Rate; **GFR:** Glomerular Filtration Rate; **PRISMA-ScR:** Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews; **NGAL:** Neutrophil Gelatinase-Associated Lipocalin; **KIM-1:** Kidney Injury Molecule-1; **L-FABP:** Liver-Type Fatty Acid-Binding Protein; **CLU:** Clusterin; **CysC:** Cystatin C; **TNFR1:** Tumor Necrosis Factor Receptor 1; **TNFR2:** Tumor Necrosis Factor Receptor 2; **sTNFR:** Soluble Tumor Necrosis Factor Receptor; **IL:** Interleukin; **IL-6:** Interleukin-6; **IL-18:** Interleukin-18; **MCP-1:** Monocyte Chemoattractant Protein-1; **TGF-β:** Transforming Growth Factor Beta; **NF-κB:** Nuclear Factor Kappa B; **Nrf2:** Nuclear Factor Erythroid 2-Related Factor 2; **TIMP-2:** Tissue Inhibitor of Metalloproteinases-2; **IGFBP7:** Insulin-Like Growth Factor Binding Protein-7; **miRNA/miR:** MicroRNA; **cfDNA:** Cell-Free DNA; **mtDNA:** Mitochondrial DNA; **AUC:** Area Under the Curve; **HR:** Hazard Ratio; **SD:** Standard Deviation; **AI:** Artificial Intelligence; **EHR:** Electronic Health Record; **ACE2:** Angiotensin-Converting Enzyme 2; **RBP4:** Retinol-Binding Protein 4; **α1MG:** Alpha-1 Microglobulin; **β2MG:** Beta-2 Microglobulin; **AER:** Albumin Excretion Rate; **T1D:** Type 1 Diabetes; **T2D:** Type 2 Diabetes; **T2DM:** Type 2 Diabetes Mellitus; **DCCT:** Diabetes Control and Complications Trial; **EDIC:** Epidemiology of Diabetes Interventions and Complications; **VA NEPHRON-D:** Veterans Affairs Nephropathy in Diabetes Study; **CACTI:** Coronary Artery Calcification in Type 1 Diabetes Study.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICS APPROVAL

Ethical approval for this study was obtained from the Saveetha Medical College and Hospital Institutional Ethics Committee Registration No: ECR-/724/Inst/TN/2015/RR-24 (IEC – Reference Number: 003/01/2026/IEC/SMCH). The approval was granted on 06 Jan 2026.

AI USED DECLARATION

AI Tool Disclosure: The authors declare that no artificial intelligence tools (including ChatGPT, DALL-E, Copilot, or similar) were used in the creation, analysis, or writing of this manuscript. All research, analysis, and composition were completed by human authors." Grammarly Premium used for grammar enhancement.

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Cite this article: Das B, Narayanaswamy R, Shruthi KR, Rayappa WDSC, Sachin BS, Choudhary AK. The Molecular Signature of Diabetic Kidney Disease: A Scoping Review of Emerging Biomarker Classes. J Young Pharm. 2026;18(2):275-85.