DOI: 10.7860/JCDR/2026/88953.23981

Review Article

Internal Medicine Section

A Narrative Review on Biomarkers of Diabetic Nephropathy: Critical Assessment of Conventional and Emerging Indicators

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ABSTRACT

Diabetic Nephropathy (DN) is the leading cause of Chronic Kidney Disease (CKD) and End-Stage Renal Disease (ESRD) worldwide, posing a major clinical and socioeconomic burden. Early diagnosis remains difficult, as conventional biomarkers such as albuminuria and estimated Glomerular Filtration Rate (eGFR) often indicate renal injury only after irreversible damage has occurred. Recent research has identified promising biomarkers linked to inflammation, tubular damage, fibrosis, metabolic imbalance, and molecular alterations, underscoring the need for updated insights into their clinical value. The present review critically examines both established and emerging biomarkers of DN, highlighting their biological relevance, diagnostic utility, and limitations. Emphasis is placed on the shortcomings of single biomarkers and the potential of multi-marker approaches that integrate clinical parameters to improve risk assessment and support personalised treatment. Emerging indicators reflecting inflammation, tubular injury, fibrosis, and metabolic dysregulation show improved sensitivity for early and normoalbuminuric stages of disease. Despite these advances, challenges in standardisation, validation, and clinical implementation persist. Addressing these gaps is essential to advance precision nephrology and improve patient outcomes in DN.

Keywords: Early diagnosis, Inflammation, Precision nephrology, Tubular injury

INTRODUCTION

The DN is a major global health burden and remains the leading cause of CKD and ESRD worldwide. The prevalence of diabetes continues to rise dramatically, particularly in regions such as the Middle East, sub-Saharan Africa, and India [1]. Beyond its clinical consequences, DN imposes a substantial economic burden due to the escalating costs of ESRD management and is associated with a marked decline in patients' quality of life [2]. Notably, DN often progresses asymptomatically, and by the time microalbuminuria, a quantitative urinary marker is detected, substantial and potentially irreversible renal damage may have already occurred [3]. Current diagnostic approaches primarily depend on the assessment of albuminuria and eGFR, however, both parameters have notable limitations. Albuminuria typically manifests at a relatively advanced stage of disease progression, may be absent in certain classical presentations of DN, and can be influenced by various physiological conditions and external factors, thereby limiting its reliability as an early diagnostic marker [4]. Consequently, these markers fail to provide timely, mechanism-specific information on renal damage, leading to delayed diagnosis and suboptimal intervention [5]. Therefore, an urgent need for sensitive, mechanism-based biomarkers capable of enabling early detection, improved risk stratification, and personalised therapeutic strategies for DN is required.

LITERATURE RESEARCH

A comprehensive literature search and selection strategy was employed to ensure transparency and methodological rigour. Preferred academic databases, including PubMed, Scopus, and Web of Science, were searched using predefined keywords and Boolean operators such as "DN," "diabetic kidney disease," "biomarkers," "early detection," "diagnosis," and "prognosis." Eligible studies included English systematic reviews, randomised and non-randomised and diagnostic observational studies. Reviews, editorials, conference abstracts, case reports, and experimental-only studies were excluded.

DISCUSSION

Pathophysiological Basis of Diabetic Nephropathy (DN):

The DN is a multifactorial microvascular complication of diabetes, driven by interconnected metabolic disturbances and structural alterations within the kidney [6]. These processes evolve progressively, leading to a gradual decline in renal function and ultimately ESRD. Understanding the underlying mechanisms is essential for identifying reliable biomarkers and therapeutic targets [7].

Chronic hyperglycaemia initiates a cascade of metabolic abnormalities central to DN pathogenesis. A major consequence is the excessive generation of Reactive Oxygen Species (ROS), resulting in sustained oxidative stress. Elevated ROS levels damage lipids, proteins, and Deoxyribonucleic Acid (DNA), thereby disrupting cellular homeostasis and renal integrity. The principal renal sources of ROS include the mitochondrial respiratory chain, Nicotinamide Adenine Dinucleotide Phosphate (NADPH) oxidases, and xanthine oxidase [8].

Renal hypoxia is another critical contributor to DN progression and may occur early in diabetes. Increased tubular oxygen consumption, mitochondrial uncoupling and microvascular dysfunction collectively impair oxygen delivery [8,9]. Hyperglycaemia, advanced glycation end products, angiotensin II, and oxidative stress activate inflammatory signalling pathways, leading to increased expression of cytokines such as Tumour Necrosis Factor-alpha (TNF-α) and Interleukin-1 beta (IL-1β). These mediators promote immune cell infiltration into the renal interstitium, accelerating extracellular matrix accumulation and fibrosis [10].

Metabolic disturbances in diabetes translate into characteristic structural lesions. Glomerular Basement Membrane (GBM) thickening is among the earliest changes, occurring even before overt

albuminuria, and reflects increased extracellular matrix deposition under hyperglycaemic conditions. Progressive mesangial expansion, driven by matrix accumulation, reduces the effective filtration surface [11]. Tubulointerstitial fibrosis, characterised by interstitial matrix deposition, tubular atrophy, and chronic inflammation, correlates strongly with renal functional decline and prognosis [12].

Podocytes are particularly vulnerable to diabetic injury. Hyperglycaemia induces podocyte hypertrophy, detachment, and apoptosis, while disruption of slit diaphragm proteins compromises glomerular barrier integrity and promotes proteinuria [13]. Endothelial dysfunction, marked by glycocalyx loss and reduced fenestrations, increases vascular permeability and contributes to albuminuria [14]. Concurrently, pericyte loss destabilises the microvasculature and promotes fibrogenesis. Activated pericytes differentiate into matrix-producing myofibroblasts, which deposit excessive extracellular matrix proteins such as collagen and fibronectin. This process drives renal fibrosis, progressively worsening kidney damage and impairing normal renal function [15].

Conventional Clinical Biomarkers of Diabetic Nephropathy (DN)

The clinical assessment of DN has traditionally relied on a limited number of conventional biomarkers that provide indirect measures of renal injury and function. Albuminuria and eGFR remain the cornerstone markers for evaluating disease progression and renal function decline. Although these markers have long guided diagnosis and disease staging, their shortcomings, particularly in early detection and prognostic precision, are now well recognised. Serum creatinine and eGFR often lack sensitivity in detecting subtle renal impairment in the early stages of DN [16].

Proteinuria and Microalbuminuria

Albuminuria remains a cornerstone marker for DN, with microalbuminuria initially introduced as an early indicator of diabetic renal damage. Its clinical significance is based on the concept that increased urinary albumin excretion reflects disruption of the glomerular filtration barrier. However, microalbuminuria frequently appears after substantial renal injury has occurred and may be absent in a subset of patients with diabetic kidney disease and reduced GFR [17]. Moreover, urinary albumin levels exhibit marked intra-individual variability influenced by physiological and external factors, limiting their reliability for monitoring disease progression. A longitudinal cohort study by Looker HC et al., (2019) specifies that the structural renal changes can precede detectable albuminuria, and the degree of albumin excretion does not consistently correlate with decline in GFR, further constraining its prognostic utility [18].

Serum Creatinine and Estimated Glomerular Filtration Rate (eGFR)

Serum Creatinine (sCr) and eGFR are essential tools for evaluating overall renal function and staging DN. They are influenced by age, sex, muscle mass, and hydration and other factors leading to underestimation in renal function, particularly in hyper-filtering patients [19]. Inter-individual variability in eGFR decline further limits personalised risk prediction, emphasising the need for more sensitive biomarkers that can detect early renal injury and predict disease progression more accurately [20].

Emerging Biomarkers of Diabetic Nephropathy (DN)

The identification of emerging biomarkers for DN has been driven by the well-recognised limitations of conventional markers, which often reflect renal injury only after irreversible structural damage has occurred. Novel biomarkers aim to enable earlier disease detection, refine risk stratification, and provide mechanistic insights into DN progression. Research has shown that several molecular and cellular changes begin much earlier in the disease process, creating the need for more sensitive and mechanism-based biomarkers. Emerging biomarkers related to inflammation, metabolic dysfunction, lipid dysregulation tubular injury, fibrosis, endothelial dysfunction, and metabolic alterations may help detect DN at earlier and even normoalbuminuric stages [21].

Inflammatory Biomarkers

Inflammation is a central contributor to DN pathogenesis, making inflammatory mediators attractive biomarker candidates. TNF-α and Interleukin-6 (IL-6) are key pro-inflammatory cytokines implicated in renal injury [12]. Lampropoulou IT et al., concluded that Albumin-to-Creatinine Ratio (ACR) showed no correlation with serum TNF-α, C-Reactive Protein (CRP), or fibrinogen, but demonstrated a strong association with urinary TNF-α, highlighting the potential role of urinary inflammatory markers in DN progression. Notably, soluble TNF receptors 1 and 2 are strongly associated with Diabetic Kidney Disease (DKD) and early structural alterations, including GBM thickening and podocyte foot process widening. Increased IL-6 levels may precede albuminuria, supporting its potential role as an early biomarker [22,23]. Mechanistically, TNF-α promotes apoptosis, inflammation, extracellular matrix accumulation, and increased albumin permeability, whereas IL-6 contributes to mesangial expansion. However, large, longitudinal studies are required to validate their clinical utility [24].

Adipokines and Metabolic Biomarkers

Adipokines link metabolic dysfunction with renal injury. Zinc-α2-Glycoprotein (ZAG) is a secreted adipokine involved in lipid mobilisation and insulin sensitivity. Sauceda L et al. compared concentrations of four inflammation-related proteins (ZAG, Reg-3a, elafin, RBP-4) in serum and aqueous humour of healthy controls and diabetic patients across stages of Diabetic Retinopathy (DR). Vascular Endothelial Growth Factor (VEGF)-A, IL-8, and IL-6 were measured in parallel as internal controls. No significant differences were observed in serum levels. In contrast, aqueous humour concentrations of ZAG, RBP-4, Reg-3a, and elafin were significantly elevated in advanced Non-Proliferative DR (NPDR) and Proliferative DR (PDR), with ZAG and RBP-4 also higher compared to nonapparent DR. Normalisation to total protein indicated that blood-retina barrier leakage only partially explained these increases. The findings suggest that elevated pro-inflammatory proteins (Reg-3a, RBP-4) may contribute to DR pathogenesis, while increased anti-inflammatory molecules (elafin, ZAG) may represent compensatory mechanisms [25].

Clinically, elevated ZAGP levels have been associated with early DN, disease progression, and kidney disease-related mortality, particularly in normoalbuminuric patients [26]. ZAGP modulates lipid metabolism through interactions with uncoupling proteins and correlates positively with adiponectin. Nonetheless, inconsistent associations with obesity and insulin resistance and limited longitudinal data constrain its translational application.

Lipid-associated Biomarkers

Lipoprotein-associated phospholipase A2 (Lp-PLA2) reflects inflammation and lipid dysregulation. Elevated plasma levels are observed in early and overt DN and correlate with fibrinogen, triglycerides, Low-Density Lipoprotein Cholesterol (LDL-C), and Glycated Haemoglobin (HbA1c) [27]. Although Lp-PLA2 shows promise for early detection and disease monitoring, its independence as a DN-specific marker and susceptibility to acute inflammatory influences remain unresolved [28].

Tubular Injury Biomarkers

Tubular injury occurs early in DN. Urinary Neutrophil Gelatinase-Associated Lipocalin (NGAL) reflects tubular stress and correlates

with CKD severity, predicting adverse outcomes. Liver-Type Fatty Acid-Binding Protein (L-FABP), expressed in proximal tubules, is released in response to hypoxia and tubular injury [29]. Urinary L-FABP can be detected before albuminuria, it predicts DN onset in normoalbuminuric patients and it correlates with disease severity and progression. The levels of Neutrophil Gelatinase-Associated Lipocalin (NGAL) and Liver-type Fatty Acid-Binding Protein (L-FABP) can also be affected by other kidney disorders and systemic inflammatory conditions, which may limit their specificity as biomarkers for DN. Also, the ability of L-FABP to consistently predict eGFR decline in all patient subsets remains debated [30]. A cross-sectional study on DN patients done by Kim SY et al., (2018) assessed the biomarker plasma NGAL (pNGAL), which is associated with tubular damage. The study showed that pNGAL levels were significantly elevated in patients with severe albuminuria ($p<0.001$) and demonstrated a moderate correlation with the severity of albuminuria ($r=0.467$; $p<0.001$) as well as GFR ($r=0.519$; $p<0.001$), indicating its association with progressive renal dysfunction [31].

Fibrosis and Structural Damage Biomarkers

Fibrosis-related biomarkers reflect DN progression. Transforming Growth Factor-β (TGF-β) and Connective Tissue Growth Factor (CTGF) are central mediators of extracellular matrix accumulation. Shaker YM et al., demonstrated that urinary and serum TGF-β1 were significantly elevated across all diabetic groups, with the highest concentrations in macroalbuminuria patients. Specifically, urinary and serum TGF-β1 showed strong positive correlations with urinary total protein ($r=0.9$ in macroalbuminuria, $r=0.9$ in microalbuminuria, $r=0.8$ in normoalbuminuria, and $r=0.89$ overall). These parallel increases with albuminuria and proteinuria underscore TGF-β1's role as a fibrogenic driver of DN [32]. Despite promising mechanistic relevance, therapeutic targeting of CTGF has faced translational challenges.

Genetic, Epigenetic and Omics-based Biomarkers

High-throughput omics technologies offer an unbiased approach to biomarker discovery. MicroRNAs show promise as regulators and indicators of DN-related pathways [33].

The CKD273 classifier provides robust, independent prognostic value in normoalbuminuric patients, identifying those at high-risk for DN and supporting its potential role in early preventive strategies. In a cohort of 737 patients with type 2 diabetes and normoalbuminuria followed for 4.1 years, 12% developed persistent microalbuminuria. Baseline CKD273 proteomic classifier independently predicted progression to microalbuminuria, with a hazard ratio of 2.5 (95% CI 1.4-4.3; $p=0.002$) and an Area Under Curve (AUC) of 0.79 (95% CI 0.75-0.84; $p<0.0001$), outperforming conventional risk factors. Risk prediction was significantly improved (relative IDI 14%, $p=0.002$; cNRI 0.10, $p=0.043$) [34], while proteins such as KIM-1 and β2-microglobulin predict rapid eGFR decline. Metabolomics has further identified early metabolic alterations associated with DKD. Colombo M et al., evaluated multiple inflammation-related biomarkers and found that KIM-1 and β2-microglobulin (B2M) were the most consistent predictors of renal decline in type 2 diabetes. Both showed standardised odds ratios ≥1.4 ($p<0.0003$) across all cohorts. When added to clinical covariates (baseline eGFR, albuminuria, age, blood pressure, diabetes duration), the combination of KIM-1 and B2M modestly improved predictive accuracy, increasing the AUC by 0.079 in SDR, 0.073 in Go-DARTS, and 0.239 in CARDS. Importantly, larger biomarker panels (Luminex, mass spectrometry, multiplatform) did not consistently enhance prediction beyond these two markers [35].

Comparative Evaluation of Biomarkers

The conventional markers, including albuminuria and eGFR, primarily detect advanced renal damage. Albuminuria, although historically regarded as an early indicator, often reflects established glomerular injury, while eGFR changes become evident only after substantial nephron loss. Consequently, their utility is greatest for disease staging and monitoring progression rather than early diagnosis. Furthermore, albuminuria is subject to marked intra-individual variability and does not consistently predict functional decline [36]. Emerging biomarkers have been developed to address these limitations by offering enhanced sensitivity at earlier disease stages and greater mechanistic specificity [Table/Fig-1] [36,37].

Despite advances in DN biomarker research, several limitations continue to hinder clinical translation. A major challenge is the lack of biomarker standardisation. Many emerging urinary and protein-based markers require stringent pre-analytical handling due to instability, and the absence of harmonised protocols for sample collection, processing, and analysis limits reproducibility across studies [37,38]. Methodological heterogeneity and the absence of validated cut-off values further complicate clinical interpretation. Practical implementation is constrained by cost, infrastructure requirements, and population variability. While some markers, such as urinary L-FABP, are cost-effective and amenable to routine testing, most omics-based approaches remain expensive and

Category	Biomarker	Sample type	Pathophysiological basis	Stage/detectable before albuminuria	Clinical utility	Key Limitations
Conventional markers	Albuminuria/ Microalbuminuria	Urine	Glomerular barrier disruption	Clinical DN (late)	Diagnosis & monitoring	Late appearance, variability, absent in normoalbuminuric DN
	Serum Creatinine	Blood	Reduced filtration capacity	Clinical DN (late)	CKD staging	Influenced by age, sex, muscle mass; late marker
	eGFR	Calculated (blood-based)	Global renal function decline	Clinical DN (late)	Disease staging & prognosis	Insensitive to early injury; underestimation in hyperfiltration
Inflammatory markers	TNF-α	Serum/Urine	Inflammation, apoptosis, ECM accumulation	Early-Advanced	Disease severity, progression monitoring	Limited specificity; influenced by systemic inflammation
	IL-6	Serum/Urine	Inflammation, mesangial expansion	Very early-Advanced; detectable before albuminuria	Early DN detection; Cardiovascular (CV) risk prediction	Elevated in systemic inflammation
	TNFR1, TNFR2	Serum	Inflammation, podocyte injury	Detectable before albuminuria	Predict early structural renal changes & DKD progression	Limited routine availability
Adipokines	Zinc-α2-glycoprotein (ZAG)	Serum/Urine	Lipid metabolism, insulin sensitivity	Early/Normoalbuminuric DN	Early kidney injury, progression	Conflicting metabolic associations; population variability
Lipid-associated markers	Lp-PLA2	Plasma	Lipid-driven inflammation, oxidation	Early-Clinical DN	Early detection, disease monitoring	Not DN-specific; affected by acute inflammation

Tubular injury markers	NGAL	Urine	Tubular stress and injury	Early-Advanced; detectable before albuminuria	Early kidney injury, prognosis	Low specificity for DN vs other CKD
	L-FABP	Urine	Tubular hypoxia, fatty acid metabolism	Very early-Advanced; detectable before albuminuria	Early DN, normoalbuminuric DN, progression	Variable prediction of eGFR decline
	KIM-1	Urine	Tubular epithelial injury	Detectable before albuminuria	Predicts rapid decline in eGFR	Limited clinical adoption
	β2-microglobulin	Urine/Serum	Tubular injury	Progressive DN	Predict rapid eGFR decline	Limited routine use
Fibrosis markers	TGF-β	Serum/Urine	ECM accumulation, fibrosis	Advanced DN	Macroalbuminuria, fibrotic progression	Limited early-stage sensitivity
	CTGF	Serum/Urine	Fibrosis, EMT, matrix synthesis	Early-Advanced	DN progression, ESRD and mortality risk	Translational and therapeutic challenges
ECM turnover markers		Serum/Urine	Matrix degradation, ECM turnover	Progressive DN	eGFR decline prediction	Limited longitudinal validation
Omics-based markers	miRNAs	Serum/Urine	Gene regulation	Detectable before albuminuria	Pathway-specific early DN detection	Lack of standardization
	Proteomic Classifier (CKD273)	Urine	Multi-pathway Molecular signature	Preclinical/Early DN; detectable before albuminuria	Predicts future Microalbuminuria	High cost; Infrastructure needs
	Metabolomic signatures	Biofluids	Metabolic dysregulation	Early DN; detectable before albuminuria	Identifies preclinical DKD changes	Reproducibility and validation gaps

[Table/Fig-1]: Conventional and emerging biomarkers of Diabetic Nephropathy (DN) [36,37].

technically demanding, restricting accessibility, particularly in low-resource settings [37]. Biomarker performance may also vary across ethnicities and comorbid conditions, as illustrated by inconsistent findings for ZAGP. Importantly, many biomarkers lack longitudinal and interventional validation. Advances in biomarker research for DN offer the potential to shift clinical practice toward earlier, more precise, and individualised patient management. Future strategies are likely to emphasise stage-specific biomarker application, recognising that distinct markers may be most informative at different phases of disease progression.

CONCLUSION(S)

The DN remains a leading cause of kidney failure, yet conventional biomarkers like albuminuria and eGFR often detect damage too late. Emerging biomarkers-such as L-FABP, NGAL, TNF-α, IL-6, and ZAGP-show promise for earlier, mechanism-based detection and risk stratification. Multi-biomarker panels integrating clinical parameters can enhance precision nephrology and guide personalised care. Therefore, early, standardised use of novel biomarkers is essential to shift DN management from late intervention to proactive prevention.

Author's Contribution: PM wrote the review article, SBR, VPN, RK, MR contributed to conceptualisation and proofreading, provided guidance during all stages, and contributed to the writing and editing of the manuscript.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Mar 22, 2026
- Manual Googling: May 13, 2026
- iThenticate Software: May 15, 2026 (2%)

ETYMOLOGY: Author Origin

EMENDATIONS: 6

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? NA
- Was informed consent obtained from the subjects involved in the study? NA
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Mar 12, 2026**
Date of Peer Review: **Apr 01, 2026**
Date of Acceptance: **May 17, 2026**
Date of Publishing: **Aug 01, 2026**