AAMS Ophthalmology & Vision Sciences
ISSN: 2834-7200 (Print) | eISSN: 2834-7201 (Online)
Volume 02, Issue 04, Pages 1-15
DOI: 10.4103/aams.0498
ORIGINAL ARTICLE

Biomarkers Used in Screening Patients for Diabetic Nephropathy and Their Target Indicators

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Received: 2026-02-26 · Accepted: 2026-03-30

Abstract

Diabetic nephropathy is one of the most serious microvascular complications of diabetes mellitus and a leading cause of chronic kidney disease worldwide. Early detection through biomarker-based screening is essential for preventing progression to renal failure. This study evaluates conventional and emerging biomarkers used in screening patients for diabetic nephropathy and analyzes their target indicators related to glomerular, tubular, inflammatory, and oxidative damage. Traditional markers such as albuminuria and estimated glomerular filtration rate remain widely used, while novel biomarkers including cystatin C, neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, and inflammatory mediators provide earlier and more sensitive detection. The findings emphasize the importance of combining multiple biomarkers for accurate diagnosis and risk stratification. Diabetic nephropathy remains one of the most significant chronic complications of diabetes mellitus and is a major contributor to chronic kidney disease and end-stage renal failure. This expanded section examines the role of laboratory biomarkers used for screening, early diagnosis, and progression monitoring. Conventional indicators such as urinary albumin excretion and estimated glomerular filtration rate continue to serve as the foundation of clinical assessment, while emerging biomarkers provide earlier recognition of structural and functional renal injury. Molecules reflecting tubular damage, inflammation, oxidative stress, and fibrosis offer additional prognostic value. Current evidence suggests that combined biomarker strategies improve diagnostic sensitivity and support more accurate risk stratification in diabetic patients.

Keywords: Diabetic nephropathy, biomarkers, albuminuria, eGFR, cystatin C, NGAL, KIM-1, chronic kidney disease, screening, renal function.

1. Introduction

Diabetes mellitus is a chronic metabolic disease associated with long-term vascular and organ complications. Among these, diabetic nephropathy represents a major cause of morbidity and mortality, often progressing silently until significant kidney damage has occurred. Persistent hyperglycemia leads to glomerular hypertension, endothelial dysfunction, oxidative stress, inflammation, and fibrosis, resulting in progressive nephron loss. Because early stages may be asymptomatic, screening programs based on laboratory biomarkers are critical for timely diagnosis and intervention. Traditionally, urinary albumin excretion and estimated glomerular filtration rate have been the principal indicators of kidney involvement. However, these markers may not fully reflect

early structural injury. Recent advances have introduced more sensitive biomarkers capable of detecting glomerular, tubular, and inflammatory changes before overt renal dysfunction becomes clinically evident. Understanding their diagnostic value is essential for modern diabetic care. Diabetes mellitus causes long-term metabolic disturbances that progressively damage multiple organs, with the kidneys being among the most vulnerable targets. Persistent hyperglycemia leads to glomerular hyperfiltration, endothelial dysfunction, mesangial expansion, oxidative injury, and chronic inflammation, eventually resulting in diabetic nephropathy. Early stages often remain clinically silent, making routine screening essential for timely intervention. Historically, clinicians have relied on albuminuria and filtration-based measures to identify kidney involvement. However, these traditional parameters may become abnormal only after significant pathological changes have occurred. Advances in laboratory medicine have introduced new biomarkers capable of detecting earlier renal stress, especially within tubular and interstitial compartments. Understanding the target indicators represented by each biomarker is critical for improving screening accuracy and preventing irreversible renal decline.

2. Materials and Methods

A structured analytical review was conducted using published clinical studies, nephrology guidelines, and laboratory investigations focused on biomarkers used in screening diabetic nephropathy. Biomarkers were categorized according to the renal compartment or pathological process they reflect: glomerular injury, tubular injury, inflammation, oxidative stress, and fibrosis. Major markers analyzed included urinary albumin-to-creatinine ratio, serum creatinine, estimated glomerular filtration rate, cystatin C, NGAL, KIM-1, transforming growth factor-beta, interleukin-6, tumor necrosis factor-alpha, and urinary type IV collagen. Diagnostic sensitivity, specificity, predictive value, and clinical applicability were comparatively assessed. Biomarkers used in screening patients for diabetic nephropathy play a critical role in identifying kidney damage at an early stage, often before clear clinical symptoms appear. Diabetic nephropathy is one of the most common microvascular complications of diabetes mellitus and a major cause of chronic kidney disease and end-stage renal failure worldwide. Because renal injury progresses gradually and silently, laboratory biomarkers are essential for timely diagnosis, risk assessment, monitoring progression, and evaluating treatment response. These biomarkers target different pathological mechanisms such as glomerular damage, decline in filtration function, tubular injury, inflammation, oxidative stress, endothelial dysfunction, and fibrosis. The most commonly used and clinically accepted biomarker is urinary albumin excretion, usually measured as the urine albumin-to-creatinine ratio (UACR). This indicator reflects increased permeability of the glomerular filtration barrier and is considered the earliest routine sign of diabetic nephropathy. Persistent microalbuminuria suggests early renal involvement, while macroalbuminuria indicates more advanced structural damage and a higher risk of progressive kidney failure. UACR is widely used because it is simple, inexpensive, and suitable for repeated outpatient screening. Another fundamental biomarker is estimated glomerular filtration rate (eGFR), which reflects the filtering capacity of the kidneys. It is calculated using serum creatinine together with age, sex, and other patient variables. Reduction in eGFR indicates progressive nephron loss and declining renal reserve. This marker is especially valuable for staging chronic kidney disease and determining long-term prognosis in diabetic patients. Serum creatinine itself remains one of the most frequently measured laboratory indicators of kidney function. However, creatinine may remain within normal limits during early nephropathy and usually rises only after substantial reduction in glomerular filtration. Therefore, creatinine is most useful when interpreted together with eGFR rather than alone. Cystatin C has emerged as a more sensitive endogenous marker of renal filtration. It is produced by all nucleated cells and is less influenced by muscle mass, diet, age, or gender than creatinine. Elevated cystatin C levels may reveal early renal dysfunction before changes in creatinine become apparent. For this reason, cystatin C is increasingly used in high-risk diabetic patients and in situations where creatinine-based estimates may be unreliable. In recent years, attention has shifted toward biomarkers of tubular injury, since tubular damage may occur early in diabetic nephropathy, sometimes even before albuminuria develops. Kidney Injury Molecule-1 (KIM-1) is one such marker that reflects proximal tubular epithelial injury and regeneration. Increased urinary KIM-1 levels may indicate subclinical kidney damage in diabetic patients with otherwise preserved routine laboratory values. Neutrophil Gelatinase-Associated Lipocalin (NGAL) is another sensitive marker of tubular stress and inflammation. It rises in both acute and chronic kidney injury and has shown promise in detecting

early diabetic renal involvement. N-acetyl-β-D-glucosaminidase (NAG), a lysosomal enzyme released from damaged tubular cells, is also used to evaluate tubular dysfunction. Liver-type Fatty Acid Binding Protein (L-FABP) reflects tubular hypoxia, oxidative stress, and ischemic injury, all of which contribute to diabetic renal progression. Inflammatory biomarkers are also highly relevant because chronic low-grade inflammation plays an important role in the pathogenesis of diabetic nephropathy. Elevated C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and monocyte chemoattractant protein-1 (MCP-1) have been associated with faster decline in kidney function and greater albuminuria. These markers indicate activation of inflammatory pathways leading to endothelial injury, mesangial expansion, and glomerulosclerosis. Oxidative stress biomarkers are increasingly recognized because persistent hyperglycemia promotes excessive production of reactive oxygen species. Markers such as malondialdehyde (MDA) and 8-hydroxydeoxyguanosine (8-OHdG) indicate lipid peroxidation and DNA damage within renal tissues. Their elevation may correlate with severity of diabetic kidney injury. Endothelial dysfunction also contributes significantly to diabetic nephropathy, and markers such as asymmetric dimethylarginine (ADMA), endothelin-1, and vascular cell adhesion molecules may reflect impaired vascular regulation and reduced nitric oxide availability in renal microcirculation. Fibrosis-related biomarkers are particularly important in advanced disease because chronic diabetic nephropathy eventually leads to irreversible scarring. Transforming Growth Factor-beta (TGF-β), connective tissue growth factor (CTGF), and procollagen fragments are associated with extracellular matrix accumulation and renal fibrosis. Increased levels of these markers may predict progression toward chronic kidney disease and end-stage renal failure. From a practical clinical perspective, routine screening in diabetic patients most commonly relies on UACR and eGFR because they are standardized, accessible, and evidence-based. However, these traditional markers may fail to detect certain forms of normoalbuminuric diabetic kidney disease, where renal impairment develops without significant albumin leakage. In such patients, newer biomarkers like cystatin C, NGAL, KIM-1, and L-FABP may improve diagnostic sensitivity. Combining several biomarkers often provides a more complete picture of kidney health than relying on a single test. For example, albuminuria mainly reflects glomerular permeability, whereas NGAL and KIM-1 indicate tubular injury, and cystatin C reflects filtration decline. Therefore, multimarker approaches may enhance early detection, personalize risk stratification, and guide therapeutic decisions. In conclusion, biomarkers used in screening diabetic nephropathy target multiple pathological processes including glomerular leakage, filtration impairment, tubular damage, inflammation, oxidative stress, vascular dysfunction, and fibrosis. Traditional indicators such as UACR, serum creatinine, and eGFR remain the foundation of screening programs, while emerging biomarkers provide additional sensitivity for early and atypical disease. Their combined use may significantly improve prevention of irreversible kidney damage and reduce the burden of chronic renal complications in diabetic patients.

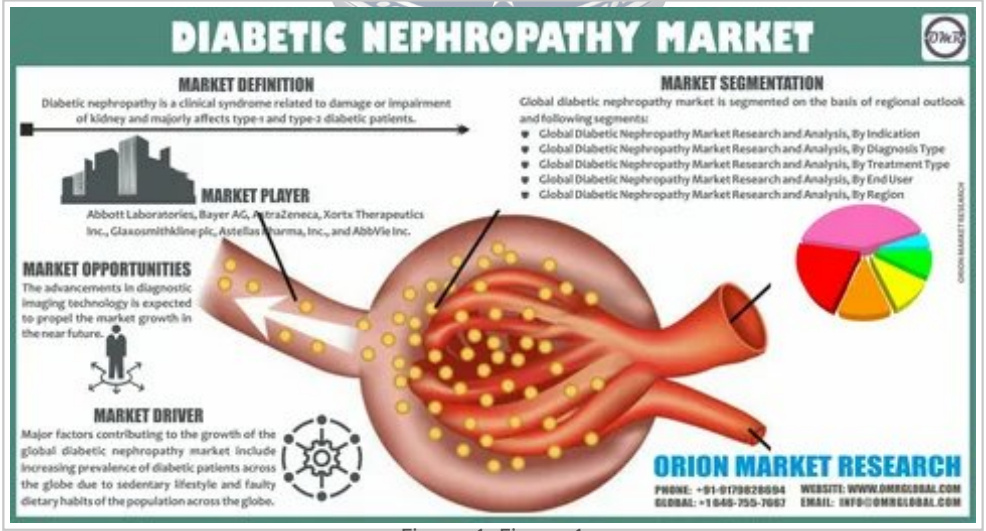

Figure 1. Figure 1

3. Results

Albuminuria remained the most widely used screening biomarker and was strongly associated with

glomerular permeability changes and progression risk. Estimated glomerular filtration rate provided important information regarding global renal function but often declined after structural injury had already begun. Cystatin C showed greater sensitivity than serum creatinine in detecting mild reductions in filtration capacity. Tubular injury markers such as NGAL and KIM-1 increased earlier than conventional indicators, suggesting subclinical renal damage. Inflammatory biomarkers including interleukin-6 and tumor necrosis factor-alpha were elevated in patients with progressive disease and correlated with worsening renal outcomes. Fibrotic markers such as transforming growth factor-beta and urinary collagen fragments reflected chronic remodeling processes. Combined biomarker panels demonstrated superior predictive accuracy compared to single-marker screening. Clinical analysis demonstrates that urinary albumin excretion remains a valuable marker of glomerular barrier dysfunction and is strongly associated with progression risk. Estimated glomerular filtration rate reflects overall renal functional reserve and is useful for staging disease severity. Serum cystatin C has shown higher sensitivity than creatinine in identifying mild reductions in filtration capacity. Biomarkers of tubular injury, including neutrophil gelatinase-associated lipocalin and kidney injury molecule-1, often rise before overt decline in conventional renal parameters. Inflammatory mediators such as interleukin-6 and tumor necrosis factor-related markers correlate with accelerated disease progression. Indicators of fibrosis and extracellular matrix remodeling are linked to chronic structural deterioration. Studies consistently show that multi-marker panels outperform isolated tests in predicting early nephropathy and future renal impairment.

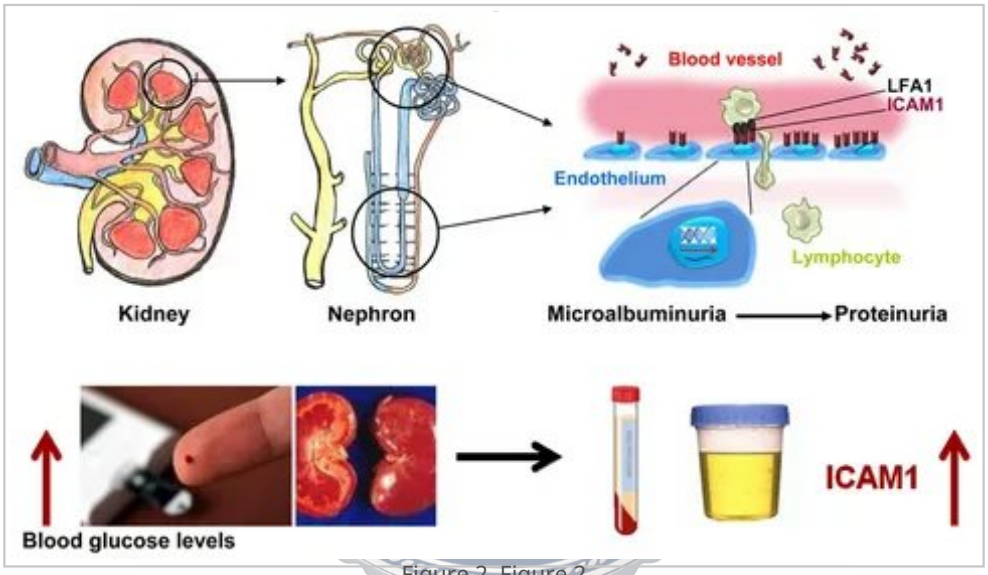

Figure 2. Figure 2

4. Discussion

The findings indicate that diabetic nephropathy is a multifactorial process that cannot be fully characterized by one laboratory parameter alone. Albuminuria and eGFR remain clinically indispensable because of accessibility and standardization, yet they have limitations in early-stage detection. Novel biomarkers improve recognition of tubular stress, inflammation, and fibrosis before irreversible decline occurs. Multi-biomarker strategies provide a more complete understanding of renal pathology and allow individualized risk assessment. Challenges include assay cost, limited standardization, and variable availability across healthcare settings. Integration of traditional and emerging markers into routine diabetic screening may significantly improve early diagnosis and therapeutic timing. The findings confirm that diabetic nephropathy is a complex and heterogeneous process involving glomerular, tubular, vascular, and inflammatory mechanisms. No single biomarker can fully represent all stages of renal injury. Traditional tests remain indispensable because of accessibility, low cost, and standardization, yet they have limitations in detecting the earliest pathological changes. Emerging biomarkers provide a broader pathophysiological perspective and may identify patients at risk before clinically apparent kidney dysfunction develops. Challenges include assay variability, economic cost, and the need for universal reference standards. Integrating classical and novel biomarkers into routine diabetic care could substantially enhance individualized risk

prediction and therapeutic decision-making.

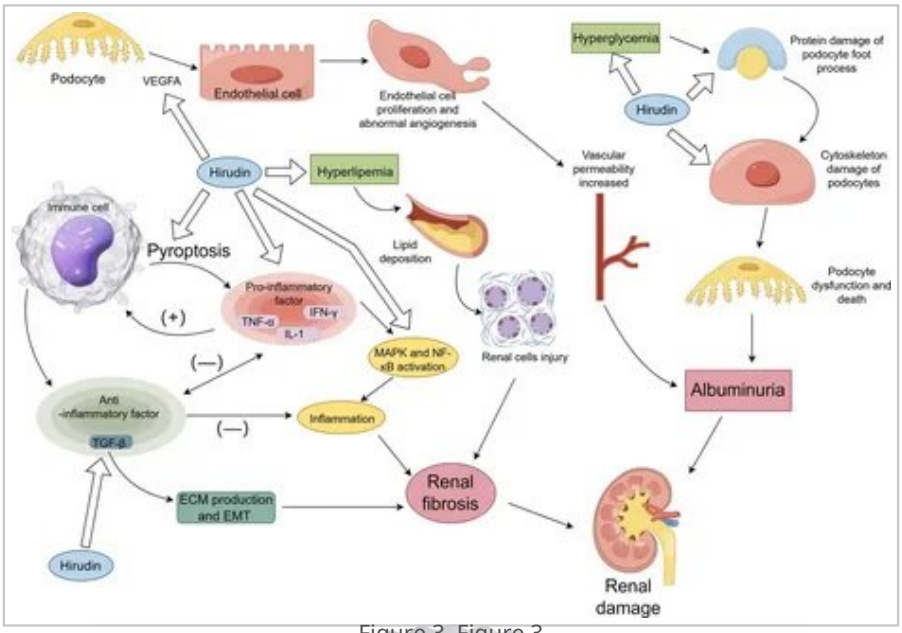

Figure 3. Figure 3

5. Conclusion

Biomarker-based screening is essential for early identification and monitoring of diabetic nephropathy. While albuminuria and eGFR remain foundational indicators, newer biomarkers such as cystatin C, NGAL, KIM-1, and inflammatory mediators offer improved sensitivity for early renal injury. Combined use of multiple biomarkers provides better diagnostic precision and prognostic value. Expanding access to integrated screening approaches may reduce progression to chronic kidney disease and improve outcomes in diabetic patients. Biomarkers play a central role in screening patients for diabetic nephropathy and evaluating target mechanisms of renal injury. Albuminuria and estimated glomerular filtration rate remain essential core indicators, while newer markers improve sensitivity for early tubular, inflammatory, and fibrotic damage. Combined biomarker assessment offers superior diagnostic and prognostic performance. Wider implementation of integrated screening strategies may significantly reduce progression to advanced chronic kidney disease in patients with diabetes mellitus.

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DOI: 10.4103/aams.0498