Combining Urinary Biomarkers and Sonographic Features for Early Detection of Diabetic Nephropathy in Type 2 Diabetes Mellitus: A Comprehensive Literature Review

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Abstract

Background:

Diabetic nephropathy (DN) is a leading microvascular complication of type 2 diabetes mellitus (T2DM) and a major contributor to chronic kidney disease and end-stage renal failure worldwide. Traditional diagnostic tools—such as albuminuria and estimated glomerular filtration rate (eGFR)—often fail to detect renal injury at a subclinical stage, thereby delaying timely intervention. Advances in molecular diagnostics and imaging have introduced new modalities that may improve early detection and risk stratification.

Objective:

This review aims to evaluate and synthesize existing evidence on the integration of urinary biomarkers and renal ultrasonographic features for the early diagnosis of DN in patients with T2DM.

Methods:

A narrative review approach was adopted to explore recent studies focused on urinary biomarkers—namely podocalyxin, kidney injury molecule-1 (KIM-1), connective tissue growth factor (CTGF), and procollagen type III N-terminal propeptide (PIIINP)—and ultrasonographic parameters such as renal size, cortical thickness, echogenicity, and resistive index (RI). The analysis includes assessment of the pathophysiologic basis, diagnostic relevance, limitations, and clinical implications of each modality.

Results:

Urinary biomarkers provide insights into early glomerular, tubular, and fibrotic changes that precede proteinuria and eGFR decline. Concurrently, ultrasound imaging yields non-invasive visualization of renal structural and hemodynamic alterations. The integration of these two domains enhances diagnostic sensitivity, facilitates better risk stratification, and allows for earlier initiation of nephroprotective therapies. However, limitations such as assay variability, operator dependency, and lack of standardized thresholds present current barriers to widespread clinical adoption.

Conclusion:

Combining urinary molecular profiling with sonographic renal assessment represents a promising strategy for the early detection and monitoring of DN in T2DM. Further validation through longitudinal, multi-center studies is needed to establish evidence-based protocols and support integration into clinical practice guidelines.

Keywords:

Diabetic nephropathy; Type 2 diabetes mellitus; Urinary biomarkers; Renal ultrasound; Podocalyxin; KIM-1; CTGF; PIIINP; Cortical thickness; Resistive index; Early detection

1. Introduction

1.1 Overview of Type 2 Diabetes Mellitus (T2DM)

Type 2 Diabetes Mellitus (T2DM), characterized by a combination of insulin resistance and inadequate insulin secretion, has emerged as one of the most prevalent chronic non-communicable diseases worldwide. Driven by rising obesity rates, sedentary behavior, and nutritional transitions, this condition has escalated to epidemic proportions, particularly in low- and middle-income countries. According to the International Diabetes Federation (IDF), the global diabetic population is projected to surpass 780 million individuals by 2045, with T2DM constituting more than 90% of these cases.[1] The chronic hyperglycemic environment associated with T2DM predisposes affected individuals to a myriad of systemic complications, including those involving the cardiovascular, nervous, and renal systems.

1.2 Burden and Pathophysiology of Diabetic Nephropathy (DN)

Among the microvascular complications of diabetes, diabetic nephropathy (DN) remains the leading cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD) globally, accounting for approximately half of all cases requiring dialysis or renal transplantation in developed nations.[2,3] DN progresses insidiously, with early pathophysiological changes including glomerular hyperfiltration, mesangial expansion, thickening of the glomerular basement membrane, and subsequent tubular atrophy and interstitial fibrosis.[4,5] These alterations ultimately

culminate in declining glomerular filtration rate (GFR), persistent proteinuria, and eventual renal failure if left unchecked.[6]

The clinical trajectory of DN often begins with a silent phase, where structural and biochemical renal alterations occur in the absence of overt clinical symptoms or changes in conventional biochemical parameters. As such, a significant opportunity for early intervention is frequently missed, underscoring the urgent need for improved tools for initial detection and risk stratification.[7]

1.3 Limitations of Traditional Diagnostic Parameters

Conventional markers widely used to identify renal dysfunction in diabetic patients—such as urinary albumin excretion, serum creatinine, and estimated glomerular filtration rate (eGFR)—have been integral to routine clinical practice but are increasingly recognized as suboptimal for detecting early-stage nephropathy. Microalbuminuria, though often regarded as the earliest clinical indicator of DN, lacks specificity and may fluctuate due to extrarenal factors such as physical activity, infection, or blood pressure variability.[8] Moreover, structural renal damage, particularly involving the glomerular and tubular compartments, may precede albuminuria or even develop in its absence.[9,10] Similarly, serum creatinine and eGFR are poor markers for early renal injury, as they typically remain within normal limits until substantial nephron loss has occurred.[11] These limitations illustrate the imperative need to explore more sensitive, specific, and non-invasive diagnostic tools capable of capturing renal abnormalities at a subclinical stage.

1.4 Emerging Paradigms: Biomarkers and Imaging in Early Nephropathy

To address current diagnostic challenges, considerable research efforts have been directed toward identifying early indicators of renal injury that surpass traditional markers in sensitivity and clinical relevance. Urinary biomarkers have attracted particular interest due to their non-invasive nature and ability to reflect dynamic pathological processes occurring within the nephron. Notably, markers such as podocalyxin—a podocyte-specific protein—flag early glomerular disruption, while Kidney Injury Molecule-1 (KIM-1) serves as a robust indicator of proximal tubular injury.[12,13] Additional contributors to the panel of promising urinary markers include Connective Tissue Growth Factor (CTGF) and Procollagen Type III N-terminal Propeptide (PIIINP), both of which signal early fibrotic activity within renal tissue.[14]

In parallel, renal ultrasonography—enhanced by Doppler imaging—has proven to be a valuable tool for assessing anatomical and hemodynamic changes associated with diabetic nephropathy. Attributes such as reduced renal cortical thickness, increased echogenicity, altered renal length, and elevated resistive index (RI) have demonstrated correlations with DN severity and progression.[15-17] These sonographic features provide a real-time, non-invasive means of evaluating structural and functional changes in the kidneys, supplementing the biochemical insights offered by urinary biomarkers.

1.5 Rationale for a Combined Diagnostic Approach

Isolated use of either urinary biomarkers or imaging modalities offers only a fragmented picture of renal health. Urinary biomarkers effectively capture molecular and cellular derangements, but may vary due to external factors and assay conditions. Meanwhile, ultrasonography enables visualization of pathological changes in renal architecture and perfusion, yet it may not detect early molecular disruptions until anatomical consequences manifest. Therefore, integrating both diagnostic avenues is posited to improve accuracy in early detection, allow for pathological cross-verification, and enable more comprehensive patient risk profiling.

A combined assessment—leveraging the strengths of both modalities—holds potential to identify renal injury at an earlier stage than either test could independently achieve. Such an approach may also facilitate more personalized surveillance strategies, improve prognostication, and guide therapeutic decisions aimed at delaying or reversing renal damage in patients with T2DM.[18,19]

1.6 Aim and Scope of the Review

This literature review endeavors to systematically explore the current evidence surrounding the use of selected urinary biomarkers—specifically podocalyxin, KIM-1, CTGF, and PIIINP—and key renal ultrasound parameters such as renal length, cortical thickness, echogenicity, and resistive index, in the early detection of diabetic nephropathy in individuals with type 2 diabetes. By evaluating the diagnostic utility, limitations, and correlation of these parameters with disease stage and progression, the review aims to highlight the potential of an integrated diagnostic model. Such a framework could redefine current clinical practices in the early identification and management of diabetic kidney injury, thereby improving long-term patient outcomes and reducing the burden of renal failure.

2. Pathophysiology of Diabetic Nephropathy

2.1 Glomerular and Tubular Alterations

Diabetic nephropathy (DN), a key microvascular complication of diabetes mellitus, results from a complex interplay of metabolic and hemodynamic derangements, which lead to progressive structural and functional alterations within the renal parenchyma. Early in its course, DN is characterized by glomerular hyperfiltration, ostensibly a compensatory mechanism driven by increased intraglomerular pressure and afferent arteriolar vasodilation.[20] Persistent hyperglycemia triggers biochemical cascades—such as activation of the polyol pathway, generation of advanced glycation end-products (AGEs), and oxidative stress—that contribute to cellular injury and inflammation.[21]

At the structural level, glomerular changes include mesangial matrix expansion, thickening of the glomerular basement membrane (GBM), and eventual glomerulosclerosis—processes that collectively compromise the glomerular filtration barrier.[22] Equally critical but often underappreciated are the alterations in the tubulointerstitial compartment. Tubular epithelial cell hypertrophy, basement membrane thickening, and tubular atrophy are commonly observed in histological specimens from patients with DN and are thought to contribute significantly to progressive renal dysfunction.[23] These changes disturb reabsorption, promote profibrotic factor release, and foster chronic inflammation independent of glomerular injury.

2.2 Podocyte Injury, Fibrosis, and Inflammatory Pathways

Podocytes—specialized epithelial cells encasing the outer aspect of the glomerular capillaries—are crucial for maintaining the integrity of the glomerular filtration barrier. Chronic hyperglycemia alters podocyte phenotype and function, leading to effacement, detachment, and apoptosis, which in turn contribute to increased permeability and proteinuria.[24] Injured podocytes also secrete soluble factors that exacerbate endothelial dysfunction and mesangial activation, perpetuating glomerular injury.

Fibrotic progression in DN is mediated by several key pathways including the Transforming Growth Factor-β (TGF-β)/Smad signaling cascade, which promotes extracellular matrix (ECM)

accumulation and inhibits its degradation.[25] Other contributors to fibrosis include Connective Tissue Growth Factor (CTGF) and plasminogen activator inhibitor-1 (PAI-1), both of which correlate with disease severity in clinical populations.[26] Simultaneously, inflammatory mediators such as nuclear factor-κB (NF-κB), interleukin-6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1) are upregulated in diabetic kidneys, contributing to immune cell infiltration and chronic low-grade inflammation.[27]

The culmination of ongoing podocyte depletion, glomerulosclerosis, interstitial inflammation, and tubulointerstitial fibrosis leads to progressive nephron loss and irreversible renal impairment.

2.3 Timeline from Subclinical Damage to Overt Proteinuria

One of the defining challenges in DN is its long latent phase wherein structural and molecular derangements occur well before any clinical manifestations arise. Histological evidence suggests that mesangial expansion and mild GBM thickening can appear within years of diabetes onset—even in patients with normoalbuminuria.[28] This subclinical stage is often marked by renal hyperfiltration and increased proximal tubular reabsorption, masking early glomerular leaks in albumin.

As renal injury progresses, the filtration barrier eventually becomes permeable, leading to microalbuminuria—a state largely considered the first clinically detectable stage of DN. However, studies have shown that albuminuria does not always correlate linearly with renal histopathology, and some patients with sustained eGFR decline never exhibit significant proteinuria.[29] Thus, the progression from normoalbuminuria to overt proteinuria and declining GFR is highly heterogeneous and underscores the need for sensitive early markers capable of detecting injury before irreversible damage occurs.

2.4 Pathophysiologic Basis for Biomarker and Imaging Changes

Given the multifaceted pathophysiology of DN, various biomarkers and imaging parameters have been explored to reflect its underlying mechanisms. Urinary biomarkers are products or indicators of renal epithelial injury, inflammatory responses, and ECM remodeling that are detectable even before major clinical changes are observed. For instance, podocalyxin—shed from damaged podocytes—indicates glomerular injury, while Kidney Injury Molecule-1 (KIM-1) is indicative of

proximal tubular injury.[30.31] Likewise, CTGF and PIIINP serve as markers of profibrotic activity tied to TGF-β signaling and ECM turnover, respectively.[32]

In parallel, imaging studies reveal pathophysiologic adaptations in the kidney's morphology and vascular dynamics. Increased renal size in early DN reflects compensatory hypertrophy and hyperfiltration, whereas cortical thinning and increased echogenicity seen in more advanced DN signify parenchymal atrophy and interstitial fibrosis.[33] Additionally, Doppler-based resistive index (RI) measurements capture hemodynamic resistance within intrarenal arteries, often elevated due to microvascular remodeling, interstitial compression, and arterial stiffening.[34] These correlates not only mirror underlying pathologies but offer real-time and non-invasive methods for disease monitoring.

Understanding these physiological underpinnings validates the rationale for using both molecular and imaging techniques in an integrated approach to early detection, thereby bridging a crucial gap in traditional diagnostics.

3. Urinary Biomarkers of Early Diabetic Nephropathy

Recent advances in diabetic renal research have led to the identification of several urinary biomarkers that outperform traditional diagnostic markers in sensitivity and specificity, particularly in the early stages of diabetic nephropathy (DN). Unlike albuminuria and serum creatinine, which often reflect late functional impairment, these biomarkers provide insights into the underlying molecular and cellular processes associated with glomerular and tubular injury, inflammation, and fibrosis. This section highlights four key urinary biomarkers—Podocalyxin, Kidney Injury Molecule-1 (KIM-1), Connective Tissue Growth Factor (CTGF), and Procollagen Type III N-terminal Propeptide (PIIINP)—with established or emerging roles in the early detection of DN.

3.1 Podocalyxin

Podocalyxin is a glycosylated transmembrane protein localized to the apical surface of podocytes. As a critical component of the glomerular filtration barrier, it contributes to maintaining podocyte polarity and slit diaphragm integrity. Early podocyte damage, a hallmark of diabetic nephropathy,

results in detachment and excretion of cytoskeletal and membrane components, among them podocalyxin, into the urine.[35]

Increased urinary excretion of podocalyxin reflects podocyte injury preceding overt proteinuria, making it a promising early biomarker for DN. Studies report elevated urinary podocalyxin levels in normoalbuminuric and microalbuminuric patients with diabetes, correlating with histological evidence of podocyte disruption.[36] Furthermore, podocalyxin quantification is non-invasive and reproducible, making it practical for longitudinal monitoring of glomerular health.

3.2 Kidney Injury Molecule-1 (KIM-1)

KIM-1 is a type I transmembrane glycoprotein that is almost undetectable in healthy kidneys but is markedly upregulated and shed into urine following proximal tubular injury. Its expression is predominantly localized to dedifferentiated tubular epithelial cells undergoing regeneration or recovering from ischemic or toxic insults.[37]

In the diabetic context, elevated urinary KIM-1 levels have been consistently demonstrated in both early and advanced stages of nephropathy, with predictive value for subsequent eGFR decline and progression to overt DN.[38] Given its minimal expression in the non-injured state, KIM-1 provides high specificity for active tubular pathology. Additionally, KIM-1 is believed to mediate phagocytosis of apoptotic cells and inflammatory modulation, underlying its association with tubular remodeling processes observed in DN.[39]

3.3 Connective Tissue Growth Factor (CTGF)

CTGF, a downstream mediator of the Transforming Growth Factor-beta (TGF-β) pathway, is a pro-fibrotic protein involved in cellular proliferation, ECM synthesis, and fibrosis. Its expression is significantly elevated in renal tissues of diabetic individuals and correlates strongly with disease progression and fibrotic burden.[40]

Urinary CTGF levels have been found to rise in the early and intermediate stages of DN, prior to GFR decline or macroalbuminuria onset. Elevated CTGF excretion has been linked to both glomerulosclerosis and tubulointerstitial fibrosis, rendering it a dual-compartment indicator of renal damage.[41] This biomarker may be particularly useful in identifying patients at risk of non-

albuminuric diabetic nephropathy, a phenotype associated with underdiagnosis and delayed therapy.

3.4 Procollagen Type III N-terminal Propeptide (PIIINP)

PIIINP is a collagen-derived peptide released during synthesis of Type III collagen, a principal component of fibrotic extracellular matrix in the kidney. Its urinary excretion reflects ongoing fibrogenesis, fine-tuning its use as a marker of progressive renal scarring associated with advanced DN.[42]

Increased urinary PIIINP concentrations have been documented in diabetic patients with both overt proteinuria and relatively preserved eGFR, indicating its utility in monitoring irreversible remodeling processes before irreversible renal function deterioration.[43] When used in conjunction with other fibrotic and inflammatory markers, PIIINP assists in constructing a more granular risk profile, especially for individuals with discordant clinical and biochemical findings.

3.5 Combined Utility of Multiple Biomarkers

While each urinary biomarker offers unique diagnostic relevance depending on its site of origin and phase of injury, solitary use may be restricted by heterogeneity in disease presentation and variability from environmental or comorbid factors. Hence, employing multiple urinary biomarkers in a panel can achieve superior diagnostic accuracy by reflecting concurrent pathophysiologic events—glomerular injury (podocalyxin), proximal tubular damage (KIM-1), fibrogenic activity (CTGF, PIIINP), and overall tissue stress.

Several studies have highlighted the improved sensitivity and specificity of multi-marker models compared to traditional indicators such as albuminuria and eGFR, especially in early or non-proteinuric DN populations.[44,45] This supports a paradigm shift toward integrative biomarker profiling for timely diagnosis, risk stratification, and treatment planning.

4. Renal Ultrasonographic Features in Diabetic Nephropathy

Ultrasound imaging is a well-established, non-invasive modality for the structural and functional assessment of renal parenchyma. Advances in high-resolution and Doppler ultrasonography have expanded its clinical utility from merely evaluating gross anatomy to offering functional insights

into renal vascular resistance, parenchymal integrity, and fibrosis. In the context of diabetes mellitus, particularly Type 2 Diabetes Mellitus (T2DM), sonographic evaluation aids in detecting changes linked to early and progressive diabetic nephropathy (DN). This section elaborates on four central ultrasonographic parameters—renal size, cortical thickness, echogenicity, and resistive index (RI)—relevant to early DN detection and clinical management.

4.1 Renal Size

Measurement of renal length or size, typically through longitudinal sonographic scanning, remains a foundational parameter in renal ultrasound. In early-stage DN, renal hypertrophy—often bilaterally symmetrical—is observed, attributed to compensatory hyperfiltration, increased renal plasma flow, and glomerular hypertrophy.[46] Enlargement of renal dimensions, especially in patients with newly diagnosed T2DM, may precede histological evidence of nephropathy.

However, renal volume is not static and tends to decline in later stages of DN as fibrosis and cortical atrophy ensue. Studies have noted reduced renal size in advanced disease stages, along with distorted renal contours, indicating irreversible parenchymal loss.[47] Thus, longitudinal comparison of renal dimensions has prognostic value, especially when correlated with biochemical markers or eGFR changes.

4.2 Cortical Thickness

Renal cortical thickness serves as a proxy for nephron mass and remains particularly sensitive to early parenchymal changes. It is measured as the distance between the renal capsule and the base of the medullary pyramid, mostly in the longitudinal plane, avoiding distorted poles. In healthy individuals, cortical thickness ranges between 7–11 mm, though subtle differences may exist based on age and body habitus.[48]

In diabetic nephropathy, cortical thinning correlates with glomerular and tubular atrophy, sclerosis, and interstitial fibrosis—hallmarks of progressive renal damage.[49] Decreasing cortical thickness has been associated with reduction in eGFR, and multiple reports have identified it as a useful structural index to predict decline in renal function, even in normoalbuminuric patients.[50] As such, cortical thickness is a reliable anatomical marker for early detection and tracking DN progression.

4.3 Renal Echogenicity

Alterations in renal echogenicity—specifically increased cortical echogenicity—are indicative of parenchymal disease. Typically, the renal cortex appears less echogenic than the liver or spleen; deviation from this implies parenchymal disorganization, including interstitial fibrosis, tubular atrophy, and proteinaceous fluid accumulation.[51]

In DN, early increases in echogenicity may emerge prior to clinical parameters such as albuminuria or eGFR decline, especially in the presence of tubular damage or inflammation. Cross-sectional studies indicate that increased echogenicity is positively associated with higher serum creatinine levels, metabolic control indices (e.g., HbA1c), and urinary protein levels.[52] However, because echogenicity assessment can be subjective and dependent on machine settings and operator expertise, it is best utilized in combination with other sonographic or biochemical indicators.

4.4 Resistive Index (RI)

Resistive Index (RI), calculated using the velocity-time profile of intrarenal arteries obtained via spectral Doppler ultrasonography, reflects arterial compliance and downstream vascular resistance. It is derived from the formula:

RI = (Peak Systolic Velocity – End Diastolic Velocity) / Peak Systolic Velocity

In normal adults, the RI ranges from 0.55 to 0.7. Elevated RIs suggest increased intrarenal vascular resistance, which may result from vascular remodeling, interstitial expansion, or elevated glomerular pressures commonly seen in diabetic nephropathy.[53]

Clinical studies have shown that diabetic patients with RIs ≥0.7 are at significantly higher risk for progression of DN and eGFR decline, independent of albuminuria status.[54] Moreover, the RI appears to correlate with histological activity scores and is thus considered a valuable adjunctive tool for monitoring renal disease, particularly in those without overt proteinuria.

4.5 Practical Implications and Diagnostic Integration

While each of these imaging parameters offers valuable diagnostic insight, their integration provides a more holistic view of renal health across varied stages of diabetic nephropathy. Renal size and cortical thickness predominantly reflect anatomical and chronic changes, while

echogenicity and RI may provide clues about ongoing pathological activity such as inflammation or ischemia.

Importantly, ultrasonography can fill diagnostic gaps in patients presenting with normal albuminuria or eGFR. By leveraging it alongside urinary biomarkers, clinicians can improve early detection rates, stratify risk more effectively, and make informed decisions about timing and intensity of interventions.

Moreover, the non-invasive, repeatable, and cost-effective nature of sonographic assessment enhances its applicability in both high-resource and primary care settings, supporting broader implementation in screening programs for high-risk diabetic populations.

5. Integration of Urinary Biomarkers and Renal Ultrasound in Early Diabetic Nephropathy

The complementary roles of urinary biomarkers and renal imaging have gained increasing recognition as essential components in the early detection and longitudinal monitoring of diabetic nephropathy (DN). Traditional reliance on albuminuria and eGFR, while clinically useful, has proven insufficient in identifying subclinical renal injury or predicting progression in normoalbuminuric individuals with type 2 diabetes mellitus (T2DM).[55] When integrated, biochemical and ultrasonographic modalities offer a multifaceted diagnostic model capable of capturing both molecular dysfunction and structural remodeling—hallmarks of DN pathogenesis.

5.1 Rationale for a Combined Diagnostic Strategy

Urinary biomarkers provide direct insight into pathophysiological processes such as podocyte detachment (podocalyxin), tubular epithelial damage (KIM-1), fibrotic progression (CTGF, PIIINP), and inflammatory activity (MCP-1, NGAL). However, their isolated interpretation may be influenced by factors unrelated to chronic kidney disease, including acute injuries, systemic inflammation, or assay variation.[56] On the other hand, ultrasonographic parameters such as renal size, cortical thickness, echogenicity, and resistive index (RI) reflect cumulative structural and hemodynamic changes across glomerular and tubulointerstitial compartments. Thus, integrating these tools allows for simultaneous assessment of early cellular damage and macroscopic anatomical adaptations, improving diagnostic sensitivity.

5.2 Diagnostic Enhancement through Multimodal Frameworks

Emerging clinical studies have demonstrated that combining urinary biomarkers with ultrasound parameters increases diagnostic accuracy and risk stratification potential for early DN. For example, elevated urinary KIM-1 and reduced cortical thickness have been associated with faster GFR decline in asymptomatic patients, suggesting a synergistic effect of combining functional and morphologic indicators.[57] Similarly, high resistive index values, when accompanied by elevated urinary CTGF or PIIINP, pinpoint active fibrotic changes that may remain undetected through GFR or albuminuria screening alone.[58]

In a multicenter study involving diabetic subjects with normoalbuminuria, patients with normal serum creatinine but increased urinary KIM-1 and echogenic kidneys on ultrasound were significantly more likely to develop microalbuminuria and GFR decline over a 3-year period compared to those with normal readings in both assessments.[59] These findings underscore the predictive superiority of incorporating both dimensions into routine nephropathy screening practices.

5.3 Clinical Pathways and Predictive Algorithms

Proposed diagnostic pathways increasingly support the use of urinary biomarkers and ultrasonographic data in defining DN phenotypes and risk categories. For instance, patients showing early biomarker elevation (e.g., KIM-1 >5.3 ng/mg Cr, CTGF > 230 pg/mg Cr) but with preserved cortical thickness and normal RI may benefit from conservative measures such as intensified glycemic control, lifestyle adjustment, and renin-angiotensin system inhibitors.[60] Conversely, individuals with both elevated biomarkers and abnormal ultrasound findings may be candidates for more aggressive intervention and close follow-up.

Diagnostic algorithms that incorporate both modalities can be adapted into clinical practice and decision-support systems. Variables such as age, diabetes duration, HbA1c, and systolic blood pressure can be integrated with urinary podocalyxin or KIM-1 levels and imaging-derived cortical thickness or RI to estimate disease probability. This aligns with the principles of predictive, preventive, and personalized (3P) medicine—key goals in chronic disease management.

5.4 Advantages and Barriers to Implementation

A dual-modality approach offers several advantages:

- Detects DN before irreversible structural damage has occurred
- Allows differentiation between glomerular and tubular sources of injury
- Enhances disease monitoring without the need for invasive biopsy
- Facilitates early therapeutic decisions and individualized care

However, barriers to implementation include cost and availability of biomarker assays in low-resource settings, the need for skilled personnel to perform and interpret ultrasonography consistently, and the lack of universal cut-off values or standardized protocols.[61] Furthermore, inter-laboratory variability in urinary biomarker measurements and differences in imaging equipment or technique can lead to inconsistencies in interpretation.

5.5 Summary and Future Potential

Despite these challenges, integrating urinary biomarkers and renal ultrasonography represents a transformative approach to managing diabetic nephropathy from its earliest stages. Ongoing research and advancements in point-of-care technologies, miniaturized ultrasound devices, and multiplex biomarker platforms may help broaden accessibility and accuracy. Ultimately, a multimodal diagnostic framework may serve as a cornerstone for future DN screening strategies that are both patient-centered and pathophysiologically informed.

6. Conclusion

Diabetic nephropathy (DN) remains a leading cause of chronic kidney disease and end-stage renal failure worldwide, particularly in patients with type 2 diabetes mellitus (T2DM). The insidious onset and heterogeneity in disease progression pose major challenges for timely diagnosis and intervention. Conventional markers such as albuminuria and serum creatinine, while historically central to DN detection and staging, exhibit delayed responsiveness and sometimes fail to reflect the extent of underlying renal pathology.

This review underscores the emerging utility of combining urinary biomarkers and renal sonographic features as a comprehensive, non-invasive model for early DN prediction and

monitoring. Urinary markers like podocalyxin, KIM-1, CTGF, and PIIINP widen the diagnostic lens by identifying glomerular, tubular, and fibrotic processes prior to functional impairment. Similarly, renal ultrasound parameters — including cortical thickness, echogenicity, renal length, and resistive index — offer insights into structural and hemodynamic alterations that accompany or precede overt nephropathy.

The integration of biochemical and imaging indicators provides a pathophysiologically - informed framework capable of enhancing diagnostic accuracy, personalizing risk prediction, and informing management strategies in patients with T2DM. Although implementation challenges exist, including lack of standardized biomarker thresholds, operator dependency in ultrasound imaging, and limitations in access or affordability, ongoing technological advancements and clinical validation efforts offer hope for broader applicability.

As healthcare systems increasingly pivot toward preventive and precision medicine, the dual approach of urinary biomarker profiling and sonographic evaluation stands poised to redefine early diabetic kidney care.

Ultimately, a multimodal diagnostic strategy, integrated into clinical workflows, offers the potential to transform DN management — enabling earlier detection, more accurate risk stratification, and timely therapeutic intervention — thereby improving renal and cardiovascular outcomes in the growing population of individuals with diabetes.

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Conflict of Interest

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