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INTEGRATIVE ANALYSIS OF PHARMACOTHERAPY, BIOMARKERS, AND BIOMEDICAL MECHANISMS IN CHRONIC KIDNEY DISEASE ASSOCIATED WITH TYPE 2 DIABETES MELLITUS

(Literature Review)

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Abstract

This article provides an integrative analysis of the mechanisms underlying chronic kidney disease associated with type 2 diabetes mellitus, contemporary pharmacotherapeutic approaches, and the diagnostic and prognostic significance of emerging biomarkers based on recent scientific evidence. Particular attention is given to the pathogenetic contribution of hyperglycemia, oxidative stress, chronic inflammation, endothelial dysfunction, glomerular and tubulointerstitial injury, and fibrosis to the development and progression of diabetic kidney disease. In addition to conventional indicators such as albuminuria and estimated glomerular filtration rate, the potential clinical value of NGAL, KIM-1, cystatin C, and biomarkers of inflammation and oxidative stress for early detection and assessment of disease progression is discussed. Current pharmacotherapeutic strategies involving SGLT2 inhibitors, mineralocorticoid receptor antagonists, GLP-1 receptor agonists, and agents targeting the renin–angiotensin–aldosterone system are evaluated with particular emphasis on their nephroprotective effects. The prospects of proteomics, metabolomics, and multi-omics technologies for identifying novel biomarkers and therapeutic targets are also considered. The available evidence suggests that integrating pharmacological, analytical, and biomedical approaches may improve early diagnosis, individualized risk stratification, and personalized treatment strategies for chronic kidney disease associated with type 2 diabetes mellitus.

Keywords: type 2 diabetes mellitus, chronic kidney disease, diabetic kidney disease, biomarkers, pharmacotherapy, SGLT2 inhibitors, NGAL, KIM-1, oxidative stress, proteomics, metabolomics.

Introduction

T2DM is one of the major causes of chronic kidney disease worldwide and is associated with progressive decline in renal function and an increased risk of cardiovascular complications [1]. The development of kidney damage in T2DM is driven

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by the interaction of hyperglycemia, hemodynamic abnormalities, oxidative stress, chronic inflammation, endothelial dysfunction, and fibrotic processes [2].

In clinical practice, albuminuria and estimated glomerular filtration rate are the principal parameters used to assess renal damage. However, their limited ability to reflect early pathological changes has increased interest in NGAL, KIM-1, cystatin C, inflammatory and oxidative stress markers, as well as proteomic and metabolomic profiles [3,4].

In the treatment of kidney disease associated with T2DM, the nephroprotective potential of SGLT2 inhibitors, mineralocorticoid receptor antagonists, and GLP-1 receptor agonists is being increasingly investigated alongside agents targeting the renin–angiotensin–aldosterone system [5,6]. Current approaches increasingly emphasize linking pharmacotherapy with the molecular mechanisms of disease and individual biomarker profiles as a promising strategy for personalized treatment.

The aim of this article is to provide an integrative analysis of biomedical mechanisms, diagnostic and prognostic biomarkers, and contemporary pharmacotherapeutic approaches in chronic kidney disease associated with T2DM.

Materials and methods

This study was conducted as an integrative literature review focusing on chronic kidney disease associated with T2DM. Relevant scientific publications were identified through searches of PubMed, Scopus, Web of Science, and Google Scholar databases. Priority was given to studies published between 2023 and 2026.

The search strategy included combinations of the following keywords: *"type 2 diabetes mellitus," "chronic kidney disease," "diabetic kidney disease," "biomarkers," "pharmacotherapy," "SGLT2 inhibitors," "GLP-1 receptor agonists," "finerenone," "NGAL," "KIM-1," "cystatin C," "oxidative stress," "inflammation," "proteomics," "metabolomics,"* and *"multi-omics."*

Original clinical studies, systematic reviews, meta-analyses, and high-quality narrative reviews addressing the pathophysiological mechanisms, diagnostic and prognostic biomarkers, or pharmacotherapeutic approaches in T2DM-associated chronic kidney disease were considered eligible. Publications unrelated to T2DM-associated kidney disease, studies focused exclusively on acute kidney injury, duplicate publications, and sources with insufficient methodological information were excluded.

The selected publications were analyzed and synthesized according to three major domains: biomedical mechanisms of kidney injury, diagnostic and prognostic biomarkers, and contemporary pharmacotherapeutic strategies. Particular attention was paid to studies integrating molecular biomarkers with disease progression and therapeutic response.

Results

The reviewed literature consistently identifies T2DM-associated chronic kidney disease as a biologically heterogeneous condition rather than a disorder driven by

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hyperglycemia alone. Across the selected studies, four closely related areas emerged as particularly relevant: progressive metabolic and inflammatory injury, limitations of conventional renal markers, expansion of molecular and omics-based diagnostics, and the development of pharmacological strategies providing protection beyond glucose lowering [7–13].

Biomedical mechanisms of kidney injury associated with T2DM

Persistent hyperglycemia remains a central initiating factor in diabetic kidney injury, but the evidence reviewed indicates that progression depends on the interaction of several pathogenic pathways. Hyperglycemia promotes advanced glycation, oxidative stress, activation of protein kinase C-related signaling, and stimulation of the renin–angiotensin–aldosterone system. These changes contribute to glomerular hyperfiltration, increased intraglomerular pressure, podocyte injury, and increased permeability of the glomerular filtration barrier [7].

The progression from early functional abnormalities to persistent structural injury is also associated with tubular and interstitial mechanisms. Increased proximal tubular reabsorption of glucose and sodium raises cellular metabolic demand and may aggravate tissue hypoxia and mitochondrial dysfunction. In parallel, excessive production of reactive oxygen species activates inflammatory signaling and enhances the effects of mediators such as TNF-α and IL-6. Prolonged activation of these processes favors extracellular matrix accumulation and progressive glomerular and tubulointerstitial fibrosis [7,8].

The reviewed studies further suggest that the biological spectrum of diabetic kidney disease extends beyond these classical mechanisms. Mitochondrial dysfunction, endoplasmic reticulum stress, impaired autophagy, ferroptosis, epigenetic alterations, and dysregulated immune-cell responses have all been implicated in disease progression [7,13]. Taken together, these observations support a network-based interpretation of T2DM-associated kidney injury in which metabolic stress, inflammation, oxidative damage, and profibrotic signaling reinforce one another rather than acting as isolated pathways.

Diagnostic and prognostic significance of biomarkers

Albuminuria and eGFR remain the principal clinical measures used to identify, stage, and monitor chronic kidney disease in patients with T2DM. Their clinical value is well established, but the reviewed literature also emphasizes their limitations. Structural and molecular renal injury may precede a clinically relevant increase in albuminuria or decline in eGFR, and renal function may deteriorate in some patients without marked albuminuria [9].

This limitation has stimulated interest in biomarkers reflecting specific components of renal injury. NGAL and KIM-1 are primarily linked to tubular damage and may provide information complementary to conventional glomerular markers. Cystatin C may improve assessment of filtration in selected clinical settings, while TNFR-1/2, TNF-α, IL-6, and other inflammatory mediators are being evaluated as indicators of inflammatory activity and disease progression [8,9].

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The reviewed evidence also points to oxidative stress markers as potentially informative components of multimarker assessment. Their value is not limited to detecting oxidative injury itself; they may also reflect biological interactions among inflammation, endothelial dysfunction, and fibrotic remodeling. For this reason, the literature increasingly favors combinations of glomerular, tubular, inflammatory, and metabolic markers rather than reliance on a single biomarker [8,9].

A key finding from this body of evidence is that emerging biomarkers are more likely to complement albuminuria and eGFR than to replace them. Their potential clinical contribution lies in refining biological characterization and risk stratification, particularly in patients whose conventional renal parameters do not fully reflect underlying disease activity.

Proteomics, metabolomics, and contemporary analytical technologies

Proteomic and metabolomic approaches expand biomarker assessment from individual analytes to broader molecular patterns. Targeted proteomics enables simultaneous evaluation of multiple proteins in blood or urine, whereas metabolomics can characterize changes in amino acids, lipids, organic acids, and metabolites involved in energy metabolism [10].

Mass spectrometry-based platforms are particularly relevant to this transition because they allow sensitive detection and quantification of multiple molecular candidates within a single analytical framework. The reviewed literature suggests that such technologies may improve characterization of disease heterogeneity by identifying combinations of molecular changes that would not be evident from conventional laboratory parameters alone [10].

Multi-omics strategies extend this concept further by integrating genomic, epigenomic, transcriptomic, proteomic, and metabolomic information. Hill et al. [11] emphasized that such integration may improve understanding of diabetic kidney disease by revealing biological differences between patients who appear clinically similar. From a clinical perspective, this creates a potential basis for earlier detection, more precise risk stratification, and prediction of therapeutic response.

However, these approaches remain substantially more developed as research tools than as routine diagnostic methods. Their clinical translation depends on whether complex molecular signatures provide reproducible and clinically meaningful information beyond established variables such as eGFR and albuminuria [9–11].

Contemporary pharmacotherapeutic approaches

The pharmacological management of T2DM-associated chronic kidney disease has evolved from a predominantly glucose-centered strategy toward broader cardiorenal protection. Glycemic control, blood pressure management, and renin–angiotensin–aldosterone system blockade remain important, but contemporary evidence supports the addition of therapies acting on complementary renal and cardiovascular pathways [7,13].

SGLT2 inhibitors represent one of the most important developments in this therapeutic shift. Their renal effects extend beyond reduction of blood glucose. By decreasing

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proximal tubular sodium and glucose reabsorption, they modify tubuloglomerular feedback, reduce intraglomerular pressure, and attenuate glomerular hyperfiltration. These mechanisms provide a biological explanation for the observed slowing of renal function decline and improvement in cardiorenal outcomes [7].

Finerenone targets a different component of diabetic kidney disease. As a non-steroidal mineralocorticoid receptor antagonist, it reduces pathological mineralocorticoid receptor signaling associated with inflammation and fibrosis. Its mechanism is therefore complementary rather than identical to that of SGLT2 inhibition [7,12].

GLP-1 receptor agonists contribute primarily through improvement in glycemic control, body weight, and cardiometabolic risk, while available evidence also indicates favorable effects on albuminuria and the trajectory of renal function [7]. These differences are clinically important because they indicate that currently available drug classes do not provide identical forms of nephroprotection.

This distinction was also evident in the 2025 network meta-analysis by Guo et al. [12], which included 39 studies and 99,599 patients with T2DM and non-dialysis chronic kidney disease. The comparative analysis showed that SGLT2 inhibitors, GLP-1 receptor agonists, and finerenone differ in their effects across metabolic, hemodynamic, and renal outcomes. The findings therefore support treatment selection according to the individual clinical and renal-risk profile rather than assuming interchangeability among these drug classes.

Integration of biomarkers and pharmacotherapy

When the findings are considered together, the literature suggests a shift from separate investigation of pathogenesis, biomarkers, and treatment toward a more integrated model. Pathogenic processes generate measurable molecular changes; analytical methods can detect these changes; and pharmacological interventions may target the same biological pathways that the biomarkers reflect [8,9,14].

This relationship can be summarized as:

pathogenic mechanism → molecular alteration → biomarker detection → risk stratification → targeted pharmacotherapy → assessment of therapeutic response.

The practical importance of this model lies in its potential to explain why patients with the same clinical diagnosis may follow different renal trajectories or respond differently to treatment. A patient with predominant hyperfiltration, inflammatory activation, or fibrotic activity may not necessarily have the same biological risk profile, even when conventional staging appears similar.

At present, however, the evidence is stronger for the prognostic potential of many emerging biomarkers than for their direct use in treatment selection. Analytical standardization, external validation, clinically meaningful cut-off values, and proof of incremental value beyond eGFR and albuminuria remain necessary before biomarker-guided pharmacotherapy can be considered routine practice [9,11].

Overall, the reviewed evidence supports a multidimensional approach to T2DM-associated chronic kidney disease. Glycemic control remains necessary, but optimal

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management increasingly requires simultaneous attention to hemodynamic, metabolic, inflammatory, oxidative, and fibrotic pathways, together with more precise characterization of individual renal risk [7–14].

Discussion

The findings of this review indicate that chronic kidney disease associated with T2DM is best understood as a heterogeneous and multifactorial disorder in which metabolic, hemodynamic, inflammatory, oxidative, and fibrotic mechanisms interact throughout disease progression. This complexity explains why conventional assessment based only on glycemic control, albuminuria, and eGFR may be insufficient to characterize the biological activity and future progression of kidney injury in individual patients [7–9].

An important implication of the reviewed evidence is the increasing distinction between clinical manifestations of kidney disease and the molecular processes that precede them. Albuminuria and eGFR remain essential for routine clinical assessment; however, these parameters primarily reflect established functional abnormalities and may not fully capture early tubular, inflammatory, or metabolic disturbances. The growing interest in NGAL, KIM-1, cystatin C, TNFR-1/2, and markers of oxidative stress reflects an attempt to identify renal injury before substantial functional deterioration occurs [8,9]. Nevertheless, the clinical utility of these biomarkers should not be considered independently of conventional parameters. Their greatest potential may lie in complementing eGFR and albuminuria rather than replacing them.

The heterogeneity of diabetic kidney disease also supports the use of multimarker rather than single-marker strategies. A single biomarker is unlikely to reflect the entire spectrum of glomerular, tubular, vascular, inflammatory, and fibrotic changes occurring in T2DM-associated kidney injury. The integration of biomarkers representing different pathogenic pathways may therefore provide more accurate risk stratification and improve identification of patients with rapidly progressive disease. Proteomic, metabolomic, and multi-omics technologies further expand this concept by enabling simultaneous assessment of multiple molecular pathways and the identification of distinct biological phenotypes within clinically similar patient populations [10,11].

From a pharmacotherapeutic perspective, the reviewed evidence demonstrates a clear transition from a glucose-centered approach toward multidimensional cardiorenal protection. SGLT2 inhibitors, finerenone, GLP-1 receptor agonists, and renin–angiotensin–aldosterone system blockers influence different but partially overlapping mechanisms of disease progression [7,12]. This provides a biological rationale for combination treatment strategies, particularly in patients with persistent albuminuria, declining eGFR, or high cardiovascular and renal risk despite standard therapy.

At the same time, the use of several pharmacological classes raises an important question: whether treatment selection can be further individualized according to the dominant pathogenic profile of a particular patient. For example, patients with pronounced inflammatory or fibrotic activity may theoretically benefit from strategies targeting these mechanisms, whereas patients with predominant glomerular hyperfiltration or metabolic abnormalities may require a different therapeutic emphasis. Although such biomarker-

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guided treatment remains insufficiently validated for routine clinical practice, it represents one of the most promising directions for precision medicine in diabetic kidney disease [8,11,14].

The relationship between biomarkers and pharmacotherapy may also be bidirectional. Biomarkers can potentially identify patients at increased risk of progression, while changes in these markers during treatment may provide additional information on therapeutic response. Consequently, future studies should evaluate not only whether a biomarker predicts renal outcomes, but also whether it can identify patients who derive greater benefit from a specific pharmacological intervention. This distinction is critical because a prognostic biomarker is not necessarily a predictive biomarker.

Another important issue is analytical standardization. Many promising biomarkers have been investigated using different biological samples, assay platforms, laboratory protocols, and threshold values, which limits comparability between studies. Mass spectrometry, targeted proteomics, and metabolomics provide high analytical sensitivity, but their routine clinical implementation requires reproducible methods, validated reference ranges, cost-effective platforms, and standardized preanalytical procedures [10,11]. Therefore, analytical validity should be considered together with biological and clinical significance when evaluating novel biomarkers.

The reviewed literature also highlights several unresolved issues. Most emerging biomarkers have not yet undergone sufficient external validation across diverse populations. Longitudinal studies directly linking biomarker dynamics with hard renal outcomes and therapeutic response remain limited. In addition, the incremental value of new biomarkers over established clinical models based on eGFR, albuminuria, blood pressure, glycemic status, and cardiovascular risk has not been consistently demonstrated [9,11].

Thus, the major scientific challenge is no longer simply to identify additional biomarkers or develop new pharmacological agents. The more relevant objective is to integrate molecular information, analytical technologies, and therapeutic strategies into a clinically applicable framework. Such an approach may allow progression from conventional disease staging toward biological phenotyping of T2DM-associated chronic kidney disease and, ultimately, toward individualized nephroprotective therapy.

Overall, the available evidence supports an integrated model in which pathogenic mechanisms determine molecular alterations, these alterations are identified through appropriate biomarkers and analytical technologies, and the resulting biological profile contributes to risk stratification and therapeutic decision-making. Further prospective studies are required to determine whether this model can improve renal outcomes beyond current standard-of-care approaches [7–14].

Conclusion

Chronic kidney disease associated with T2DM is a complex multifactorial condition driven by the interaction of metabolic, hemodynamic, inflammatory, oxidative, and fibrotic mechanisms. Current evidence indicates that conventional indicators such as albuminuria and eGFR remain essential for clinical assessment, but their diagnostic and prognostic value may be strengthened by emerging biomarkers, including NGAL, KIM-1, cystatin C,

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inflammatory mediators, and molecular profiles derived from proteomic and metabolomic analyses.

The integration of biomedical mechanisms, analytical biomarkers, and contemporary pharmacotherapy provides a promising framework for more precise risk stratification and individualized management of patients with T2DM-associated chronic kidney disease. SGLT2 inhibitors, GLP-1 receptor agonists, finerenone, and renin–angiotensin–aldosterone system blockers offer complementary nephroprotective effects, while multi-omics technologies may facilitate the identification of molecular phenotypes and novel therapeutic targets. Further prospective and standardized studies are required to validate biomarker-guided treatment strategies and determine their additional clinical value beyond conventional approaches.

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