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SYSTEMATIC REVIEW

Experimental Approaches to Diabetic Nephropathy: Cellular Models, Inducing Agents, and Pathophysiological Mechanisms

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ABSTRACT

A chronic metabolic disease known as diabetes mellitus (DM) can be caused by either impaired insulin sensitivity or inadequate insulin synthesis. Elevated blood sugar levels are a symptom of this illness, which disrupts the body's normal digestion of proteins, lipids, and carbohydrates. Systemic consequences such as retinopathy, neuropathy, nephropathy, and cardiovascular disease result from chronic hyperglycemia, making diabetes mellitus the main cause of endocrine morbidity worldwide. Nephropathy, or diabetic nephropathy, is a serious microvascular complication of diabetes. It is well-known to contribute significantly to chronic kidney disease and end-stage renal failure. Glucose transporter-1 (GLUT1) upregulation, polyol and hexosamine pathway activation, advanced glycation end product (AGE) accumulation, protein kinase C (PKC) signalling, oxidative stress, and renin-angiotensin system (RAS) activation are all mechanisms that contribute to diabetic nephropathy (DN). When these routes come together, they promote glomerulosclerosis, interstitial fibrosis, and mesangial enlargement. There are large racial and ethnic differences in the risk of diabetic nephropathy, and the prevalence of diabetes is rapidly increasing worldwide, according to epidemiological data, especially in low- and middle-income countries. The molecular underpinnings of diabetic nephropathy (DN) and therapeutic approaches have been greatly elucidated by experimental models, including *in vitro* β cell lines and *in vivo* induction using agents such as streptozotocin, alloxan, high-fat diets, and combined HFD-STZ regimens.

Keywords: Diabetic nephropathy, Diabetes mellitus, Kidney Disease, High-fat diet, Hyperglycemia, Streptozotocin

INTRODUCTION

Inadequate insulin secretion or diminished insulin effectiveness, or both, characterize diabetes mellitus (DM), a metabolic disease. Chronic hyperglycemia, caused by this malfunction, interferes with the body's natural metabolism of carbs, lipids, and proteins[1-4].

Diabetes retinopathy, neuropathy, nephropathy, cardiovascular disease, diabetic foot ulcers, and other complications can develop from chronically elevated blood sugar levels[5-7]. These complications illustrate the systemic effects of diabetes and the fact that various forms of the disease can bring about distinct health issues[8-10]. Now, diabetes mellitus (DM) ranks higher than any other endocrine illness on a global scale[11-14]. More than 200

million people would have diabetes by 2010, according to earlier epidemiological predictions, and that number was predicted to rise to 300 million by 2025[15]. Persistent hyperglycemia and glucose intolerance are hallmarks of diabetes mellitus (DM), a metabolic condition that can develop from inadequate insulin synthesis, impaired insulin action, or both[16]. A big public health concern, the prevalence of diabetes has been steadily rising over the world. Nearly 8.3% of the global population, or over 366 million individuals, were diabetic in 2011, according to the International Diabetes Federation (IDF) Diabetes Atlas. Forecasts indicate that by 2030, the figure will have risen to 552 million, with India and China accounting for over half of the additional cases. The impact of the diabetes epidemic is likely to be greater on nations with lower and intermediate incomes than on those with higher incomes[17]. A projected 1.7-fold annual increase in the world population is outpaced by a 2.7% annual increase in the prevalence of diabetes. A little over 11.3 percent of American adults (or around 25.6 million people) had diabetes in 2011, and that number was rising sharply among the elderly (26.9 percent among those 65 and up). Globally, these tendencies indicate that diabetes is on the rise, highlighting the need for improved methods of prevention, diagnosis, and treatment[18]. Worldwide, the prevalence of diabetes mellitus has been on the rise, and projections indicate that it will reach 5.4% in 2025, up from 4% in 1995. The greatest rates of diabetes diagnosis are seen in 19 countries, including the United States, China, and India[19]. Worldwide, hospitalizations due to acute and chronic illness consequences are substantial. Microvascular and macrovascular problems are more common in Asians than in Europeans when diabetes is first diagnosed[20].

This suggests that certain ethnic groups may experience an earlier and maybe more severe onset of sickness, which could have major consequences for approaches to screening and treatment. The impact on kidney function is one of the most significant consequences of diabetes. About 44% of newly diagnosed cases of renal failure are caused by diabetes, making it the major cause[21]. Diabetics still run the risk of developing chronic kidney disease (CKD), which can lead to end-stage renal disease (ESRD), even when their blood glucose levels are well managed. More than 180,000 Americans experience kidney failure as a direct result of their diabetes, which affects more than 24 million people in the United States (US)[22].

According to epidemiological research, the prevalence of diabetic nephropathy varies considerably among geographic regions and ethnic groups[23]. Compared to the 22.3% rate observed among Asian Indians in the (United Kingdome) UK, the reported rates in Vellore, India, are 8.9%, and in Chennai, 5.5%. Twenty-three percent of people with chronic renal failure have diabetic nephropathy, twenty-three percent have chronic interstitial nephritis, and seventeen percent have chronic glomerulonephritis. The significance of diabetes-related kidney complications in clinical nephrology is demonstrated by this[24].

One of the most common microvascular complications in people receiving renal replacement treatment is diabetic nephropathy (DN), which is also the main cause of chronic kidney injury[25]. About 40% of people with type 1 or type 2 diabetes mellitus (T1DM or T2DM) experience it, and it is associated with a much higher risk of death, especially from cardiovascular problems[26]. Elevated urinary albumin excretion (UAE) in the lack of other major renal diseases is a clinical hallmark of diabetic nephropathy (DN). Common symptoms include high blood pressure that does not go down, protein in urine that gets worse over time, and a general decline in kidney function[27]. Impaired kidney function is a hallmark of diabetic renal disease, which is characterized by inadequate albumin excretion[28]. At the beginning of diabetic nephropathy (DN), there is chronic microalbuminuria, which is characterized by an albumin excretion rate of 20-200 µg/min or 30-300 mg in a 24-hour period, confirmed by at least two independent tests[29]. Recent years have seen significant advancements in the study of diabetic nephropathy (DN), both in terms of biology and epidemiology, which bodes well for the future. Understanding the process by which the disease develops. Diabetic nephropathy (DN) is primarily caused by chronic hyperglycemia; however, metabolic and hemodynamic complications, among others, might influence its course through a combination of sequential and concurrent pathways. Because it regulates the uptake of glucose by renal cells, glucose transporter-1 (GLUT-1) plays an important role in the development of diabetic nephropathy (DN). When glucose levels within cells are too high, it triggers a cascade of detrimental events, such as non-enzymatic glycation, the polyol pathway, and protein kinase C activation. These pathways significantly affect the appearance and function of the kidneys. Both short-term and long-term changes in blood pressure and renal hemodynamics are linked to these metabolic disturbances; these changes worsen the course of nephropathy by altering growth factors and regulators of the albumin excretion rate (AER) and the glomerular filtration rate (GFR)[30]. New models provide a two-dimensional structure for how diabetic nephropathy develops. Initially, changes in AER and GFR can occur separately, but as the disease progresses, these metrics become increasingly intertwined. Albuminuria reductions observed with antihypertensive treatment demonstrate the progressive nature of AER and GFR changes as illness progresses[30].Findings from community-based research, such as the PREVEND and AusDiab cohorts, indicate that high-performance liquid chromatography (HPLC) may detect higher albumin levels in individuals with normal albumin levels, including those without diabetes[31]. In normal humans, the HPLC profile shows that albumin accounts for around 70% of the albumin peak, with the remaining 30% comprising globulins such as

transferrin and alpha-1 glycoprotein. The results highlight the need for clearer criteria to distinguish normo-albuminuria, microalbuminuria, and macroalbuminuria, particularly during extended monitoring, and the difficulty of interpreting albuminuria[32].

MECHANISMS OF DIABETIC NEPHROPATHY

Overexpression of GLUT-1 is considered an early event in diabetic nephropathy, as it promotes excessive extracellular matrix (ECM) production in mesangial cells and contributes to the initial structural remodeling of the diabetic kidney. Under hyperglycemic conditions, intracellular glucose is diverted to alternative metabolic pathways, thereby intensifying cellular stress. Increased flux through the polyol pathway leads to sorbitol accumulation, NADPH depletion, and oxidative stress, whereas activation of the hexosamine pathway generates glucosamine-6-phosphate, which modifies ECM-related gene promoters, including TGF-β1. At the same time, elevated intracellular diacylglycerol (DAG) activates protein kinase C (PKC) signaling, further amplifying injurious responses[33.34]. The formation and accumulation of advanced glycation end products (AGEs) represent another major pathogenic mechanism. These compounds arise from non-enzymatic glycation and progressively accumulate in renal tissues. Their interaction with RAGE activates downstream signaling through PKC, mitogen-activated protein kinases (MAPKs), and NF-κB, leading to increased synthesis of collagen I, collagen IV, and fibronectin, while reducing matrix degradation through TIMPs. AGE–RAGE signaling also enhances inflammation and reactive oxygen species (ROS) generation, thereby accelerating renal injury[35-37].

PKC activation itself has an important pathogenic role. DAG and ROS stimulate PKC isoforms, particularly PKC-β, which in turn increase the expression of endothelin-1, VEGF, and TGF-β1, while reducing nitric oxide (NO) availability and promoting endothelial dysfunction. PKC also enhances inflammatory mediators such as NF-κB and PAI-1, and PKC inhibition with agents such as ruboxistaurin has shown renoprotective effects in experimental studies[38]. Among fibrogenic pathways, TGF-β signaling occupies a central position. Activated by AGEs, ROS, DAG, angiotensin II (Ang II), and mechanical stress, TGF-β drives ECM accumulation and fibrosis through Smad2/3–Smad4 signaling, with additional cross-talk involving ERK, JNK, p38 MAPK, and AP-1. TGF-β also induces CTGF, thereby intensifying fibrotic responses[39-41].

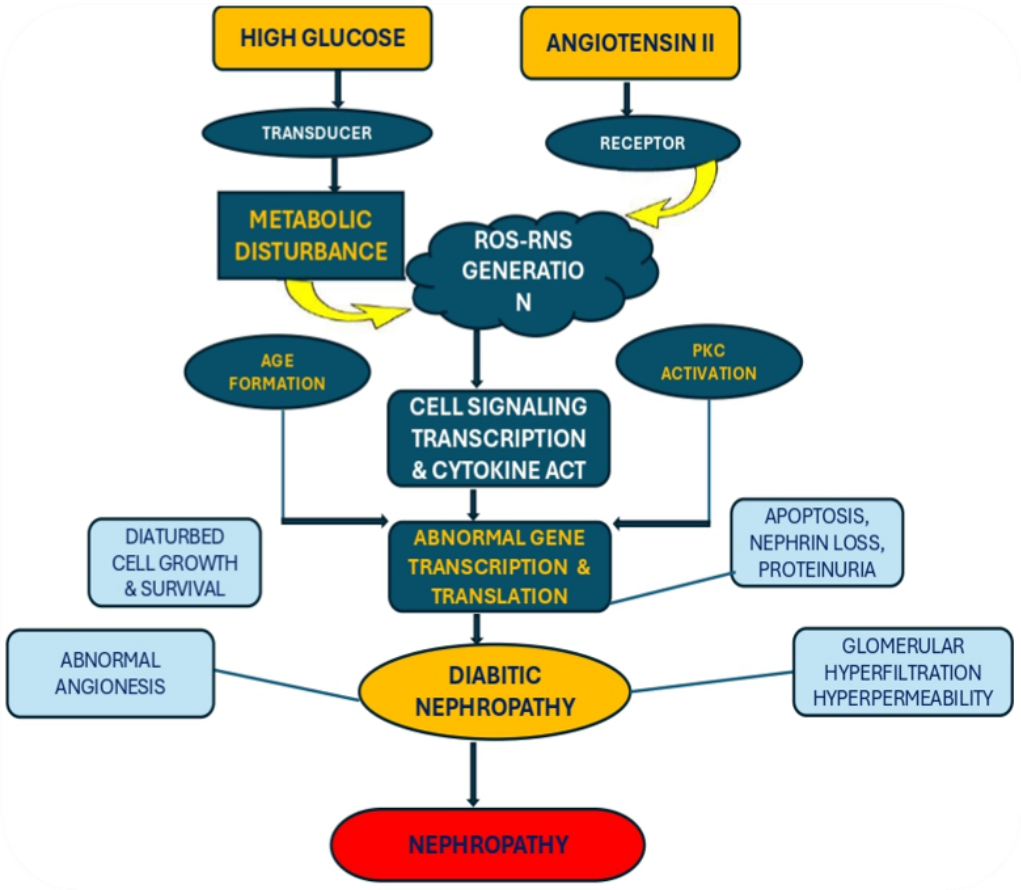

Fig. 1: Pathophysiological Mechanism of Diabetic Nephropathy

ROS generated by the mitochondrial electron transport chain and NADPH oxidase, particularly Nox4, intensify metabolic stress, inhibit GAPDH, and contribute to nitroso-redox imbalance, tubular injury, podocyte apoptosis, and interstitial fibrosis[44]. The intrarenal renin–angiotensin system (RAS) further aggravates injury by increasing TGF-β, CTGF, IL-6, VEGF, and MCP-1, raising glomerular capillary pressure, and promoting ROS generation, inflammation, and ECM accumulation; therapeutic benefit from ACE inhibitors and ARBs underscores its central importance[42-46]. Hemodynamic stress, podocyte loss, activation of Ras/Rho GTPases, and altered cell cycle regulation through p27^Kip1 and p21^Cip1 further contribute to proteinuria, matrix expansion, and progressive nephron loss[47-55].

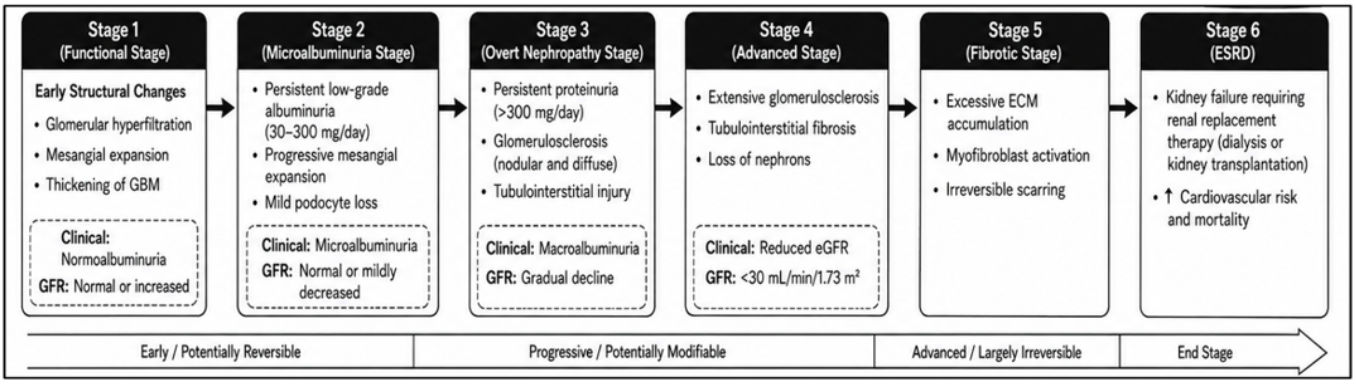

Fig. 2: Progression of Diabetic Nephropathy from Hyperglycemia to ESRD

***In vitro* models**

Cell line	Cell origin	species	Mechanism	References
MIN6	Insulinoma	Mouse	SV40 T-antigen-transformed β-cell expressing glucokinase & GLUT2	57
HIT	Insulinoma	Hamster	Secretes insulin in response to glucose via membrane-bound insulin granules & GLUT2-mediated uptake.	56
βTC1	Insulinoma	Mouse	Insulin release is mainly via hexokinase metabolism, lacking a normal glucose threshold response.	58
CRI-G1	Insulinoma	Human	Mixed hormone secretion; impaired GSIS (glucose stimulated insulin secretion studies).	59
INS1	Insulinoma	Rat	Glucokinase-dependent pathway; excellent for GSIS.	60
RINm	Radiation -induced	Rat	Secretion becomes impaired with passage; inappropriate regulation of KATP channel.	61
RINm5F	Radiation -induced	Rat	Inappropriate glucose sensitivity due to defective GLUT2/ phosphorylation	61
RINr	Radiation -induced	Rat	Abnormal glucose transporter/ phosphorylation pathways	61
βHC	Hyperplastic islets	Mouse	Early passages use glucokinase-dependent pathway; later dominated by hexokinase metabolism.	62
NIT-1	N0T2 transgenic mouse	Mouse	Secretion uncoupled from glucose; insulin released spontaneously	63
BRIN-BD11	Electrofusion-generated rat insulinoma	Rat	Physiological pathways: glucose metabolism → ATP ↑ → KATP closure → Ca^{2+} influx → insulin	64
Blox5	Fetal pancreas	Human	Normal β-cell glucose sensing pathway via glucokinase.	65, 66

AGENTS EMPLOYED TO INDUCE DIABETIC NEPHROPATHY

Medications like streptozotocin (STZ), alloxan, and a high-fat diet are commonly used to make animals develop diabetes for scientific studies. A shortage of insulin and, ultimately, elevated blood sugar levels are caused by these medications' damage to pancreatic β-cells. To study diabetes-related complications, such as nephropathy, these models are crucial. Different strains of mice show different degrees of tissue damage because of differences in their genes. Severe increases in blood creatinine and albuminuria, as well as histological changes similar to diabetic nephropathy, are common in STZ-induced type 1 diabetic mice[85].

1. Chemical induced

i. Streptozotocin:
Mechanism: Enters β-cells through GLUT2 → DNA alkylation/fragments → PARP activation → NAD^+/ATP depletion → β-cell death → insulin deficiency → sustained hyperglycemia. It can also directly damage the DNA in the proximal tubules, which can lead to renal tubular toxicity.

Features: Type 1 diabetes causes kidney abnormalities, including proteinuria, enlarged glomeruli, increased mesangial matrix, and thickened glomerular basement membrane. These modifications have the potential to cause tubulointerstitial damage over time. The extent to which these pathological changes occur is primarily determined by the dosage, animal species, and study duration[86].

ii. Alloxan:
Mechanism: It infiltrates β-cells (via GLUT2) and undergoes redox cycling, leading to the generation of ROS, hydroxyl radicals, oxidative stress, DNA damage, and cellular death. This causes β-cell death and elevated blood glucose levels.

Features of DN include hyperglycemia, glucosuria, polyphagia, hyperlipidemia, and renal abnormalities such as mesangial enlargement and increasing basement membrane thickening, which are all signs of type 1-like diabetes[87].

iii. Cisplatin:

Mechanism: Through organic cation transporters, it builds up in renal tubular epithelial cells, particularly proximal tubules, and causes nephrotoxicity by producing ROS, mitochondrial dysfunction, inflammation, and DNA damage. Renal cells undergo necrosis and apoptosis as a result. It is frequently used to cause kidney damage that resembles some of the clinical characteristics of diabetic nephropathy, such as oxidative stress and tubular damage, even though it does not directly cause diabetes.

Features of DN Produced: Causes tubular necrosis, inflammation, oxidative stress, fibrosis, and increased blood creatinine and urea, all of which are signs of renal failure. Histological alterations resembling nephropathy include tubular degeneration, interstitial inflammation, and reduced renal function[88].

iv. Streptozotocin + Nicotinamide:

Mechanism: While streptozotocin causes modest β-cell damage, nicotinamide partially protects pancreatic β-cells by inhibiting PARP and lowering oxidative stress. This combination mimics Type 2 diabetes conditions by causing insulin resistance and partial insulin shortage.

Features of DN Produced: Causes Type 2-like diabetes, which is marked by dyslipidemia, poor glucose tolerance, and mild hyperglycemia. Mild to moderate albuminuria, thickening of the glomerular basement membrane, growth of the mesangial matrix, and progressive nephropathy are examples of renal symptoms[89].

2. Diet-induced

i. High Fat Diet:

Mechanism: A high-fat diet precipitates oxidative stress, inflammation, insulin resistance, dyslipidemia, obesity, and compensatory hyperinsulinemia, ultimately leading to β-cell failure.

Features of DN: Diabetic nephropathy (DN) is characterized by a phenotype linked to Type 2 diabetes, which includes glomerular hypertrophy, mesangial expansion, basement membrane thickening, albuminuria, and interstitial inflammation[90].

3. Diet+Chemical induced

HFD+STZ:
Mechanism: A high-fat diet (HFD) is utilized to induce insulin resistance initially. A small amount of streptozotocin (STZ) is then administered to partially impair β-cell function. This yields a hybrid model with features of both insulin resistance and β-cell insufficiency.

Features of DN Produces: The combined model better mimics the progression of human type 2 diabetes. It results in hyperglycemia, albuminuria, glomerular and tubular lesions. The kidney histopathology shows glomerular basement membrane thickening, mesangial expansion, etc[90].

IMPORTANCE OF EXPERIMENTAL MODELS IN TRANSLATIONAL RESEARCH

- **Molecular Mechanism Discovery:** *In vitro* β cell lines and *in vivo* rodent models allow researchers to dissect pathways such as oxidative stress, inflammation,

advanced glycation end-products (AGEs), and renin–angiotensin system activation. These mechanisms are central to DN progression and can be studied in controlled environments[67-70].

- **Therapeutic Target Validation:** Models induced by streptozotocin (STZ), alloxan, or high-fat diets mimic type 1 and type 2 diabetes, respectively. They provide platforms to test interventions such as SGLT2 inhibitors, ACE inhibitors, and novel anti-fibrotic agents before moving to clinical trials[71, 72].
- **Pathophysiological Relevance:** Rodent models reproduce hallmark DN features: albuminuria, glomerular basement membrane thickening, mesangial expansion, and tubulointerstitial fibrosis. This allows researchers to correlate molecular changes with histological and functional outcomes[73].
- **Human Translation:** Comparative studies between animal models and human biopsies reveal overlapping and cell-type-specific mechanisms, ensuring that findings are clinically relevant[74, 75].

LIMITATIONS OF CURRENT EXPERIMENTAL MODELS OF DIABETIC NEPHROPATHY

Despite the widespread use of *in vitro* β-cell systems and *in vivo* induction models, including streptozotocin (STZ), alloxan, high-fat diet (HFD), and HFD+STZ protocols, several limitations continue to compromise their translational value in diabetic nephropathy (DN) research. A major concern is that no single model fully captures the complex pathophysiology of human DN, which arises from interactions among metabolic, inflammatory, and hemodynamic disturbances. Even the more established rodent models capture only part of the disease spectrum and generally reflect the early manifestations of DN, such as mesangial expansion, rather than the advanced fibrosis and end-stage renal disease (ESRD)-like lesions observed in humans[76, 77].

Species-related differences further widen the translational gap. Rodents differ substantially from humans in immune responses, renal hemodynamics, and drug metabolism, factors that may alter both disease progression and therapeutic responsiveness and likely contribute to the failure of many encouraging preclinical therapies in later clinical studies[78].

Chemically induced models also have inherent shortcomings. STZ and alloxan predominantly induce type 1 diabetes through β-cell toxicity and therefore do not adequately represent the insulin resistance and metabolic syndrome that characterize type 2 DN. Their outcomes may also vary considerably depending on dose, route, and protocol. STZ may directly damage renal tissue, whereas alloxan-induced diabetes can, in some cases, be reversible, thereby reducing experimental consistency[79].

HFD-induced models more closely reflect metabolic syndrome, yet they often produce only mild or slowly progressive renal injury, with limited albuminuria and glomerulosclerosis. Combined HFD+STZ models offer an improved approximation of type 2 diabetes progression, but reproducibility remains variable and mortality may be high in some study designs[80]. Conventional *in vitro* models are similarly restricted by their inability to replicate the multicellular kidney microenvironment, hemodynamic stress, immune responses, and fibrosis progression, while primary cells tend to lose their native phenotype during prolonged culture. Kidney organoids are more physiologically relevant, but incomplete maturation, limited nephron segmentation, lack of vascular and immune integration, and absence of flow-related mechanical stimuli still constrain their utility[78-84].

FUTURE PROSPECTS OF ADVANCED DIABETIC NEPHROPATHY MODELS

The need for improved experimental models of diabetic nephropathy (DN) remains a recurring theme in recent literature, reflecting the limitations of current approaches in replicating advanced human disease. Contemporary DN and diabetic kidney disease (DKD) models, although widely used, do not fully capture the complex pathological features observed in clinical settings. A 2025 narrative review of murine models highlights that existing systems reproduce certain structural changes but fail to capture the severity and progression of human DN, underscoring the need for more refined, clinically relevant models. Similarly, the CORDIS project on three-dimensional kidney organoids identifies the lack of a comprehensive preclinical system capable of reproducing the functional, structural, and molecular characteristics of advanced DN as a major obstacle to therapeutic development[91]. The current landscape of advanced disease modeling is evolving beyond classical approaches and can be broadly categorized into four major tiers. Rodent models, including pharmacological, genetic, diet-induced, and combined approaches, remain essential for studying disease progression at a whole-organism level, although their limitations in reproducing advanced human pathology are well recognized. Two-dimensional (2D) cell culture systems offer experimental simplicity and cost-effectiveness, but their inability to replicate multicellular interactions and long-term tissue remodeling limits their utility. In contrast, three-dimensional (3D) kidney organoids are emerging as a promising platform that bridges the gap between simplified *in vitro* systems and *in vivo* models, while also reducing species-dependent differences. These systems have been identified as valuable tools for investigating disease mechanisms and screening potential therapeutics[92]. Furthermore, bioengineered and systems-based models are increasingly being recognized for their ability to provide a more physiologically relevant environment for studying diabetic complications. Among these advances, the development of human-relevant

organoid systems represents the most significant future direction. Human stem cell–derived kidney organoids offer the potential to reproduce fibrosis, metabolic stress, and molecular signatures associated with advanced DKD. Such models are particularly valuable because they can capture human-specific pathways that are often absent in rodent systems and may allow earlier and more effective evaluation of antifibrotic, anti-inflammatory, and metabolic therapies[91]. In addition, these systems align closely with precision medicine strategies, especially when combined with patient-derived cells and molecular phenotyping[93]. A parallel development is the increasing emphasis on precision phenotyping, in which experimental models are no longer evaluated solely by conventional markers such as albuminuria or histology. Advances in multi-omics technologies, including single-cell RNA sequencing, spatial transcriptomics, and metabolomics, have revealed the complexity of cellular heterogeneity, immune dysregulation, and metabolic reprogramming in DKD[93]. Consequently, future models are expected to be validated using cell-type–specific transcriptional profiles, spatial remodeling patterns, and pathways associated with fibrosis and inflammation[94, 95].

CONCLUSION

Diabetes mellitus is a major global health issue marked by chronic hyperglycemia resulting from insulin deficiency or resistance. One of its most severe complications, diabetic nephropathy, is a leading cause of kidney failure. It develops through complex mechanisms involving oxidative stress, advanced glycation, and activation of the renin-angiotensin system. Experimental models help in understanding its pathogenesis and developing new therapies. Early detection and good glycemic control are vital to prevent disease progression.

DISCLOSURE

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List of Abbreviations

ACE	Angiotensin Converting Enzyme
ADA	Adenosine Deaminase
AER	Albumin Excretion Rate
AGE	Advanced Glycation End Products
ALT	Alanine Aminotransferase
ARB	Angiotensin Receptor Blocker
ATP	Adenosine Triphosphate
CDK	Cyclin-Dependent Kinase
CKD	Chronic Kidney Disease
CREB	cAMP Response Element-Binding Protein
CTGF	Connective Tissue Growth Factor
DAG	Diacylglycerol
DM	Diabetes Mellitus
DN	Diabetic Nephropathy
DNA	Deoxyribonucleic Acid
ECM	Extracellular Matrix
ERK	Extracellular Signal-regulated Kinase
ESRD	End-Stage Renal Disease
FIG	Figure
GAPDH	Glyceraldehyde-3-Phosphate Dehydrogenase
GFR	Glomerular Filtration Rate
GLUT	Glucose Transporter
GSIS	Glucose Stimulated Insulin Secretion Studies
GTP	Guanosine Triphosphate
HFD	High Fat Diet
HIT	Heparin-Induced Thrombocytopenia
HPLC	High-Performance Liquid Chromatography
IDF	International Diabetes Federation
KATP	ATP-sensitive potassium channels
MAPK	Mitogen-Activated Protein Kinase
NADPH	Nicotinamide Adenine Dinucleotide Phosphate
PAI	Plasminogen Activator Inhibitor
PARP	Poly (ADP-ribose) Polymerase
PKC	Protein Kinase C
RAGE	Receptor for Advanced Glycation End-products
RAS	Renin-Angiotensin System
ROS	Reactive Oxygen Species
STZ	Streptozotocin
TGF	Transforming Growth Factor
UAE	Urinary Albumin Excretion
UK	United Kingdome
US	United States

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