Review Article
AMERICAN JOURNAL OF PHARMACY AND HEALTH RESEARCH
www.ajphr.com
2026, Volume 14, Issue 11
ISSN: 2321–3647(online)

Molecular Mechanisms in the Pathogenesis of Diabetic Nephropathy: Historical Development, Intracellular Signalling Pathways, Molecular Targets and Contemporary Therapeutic Strategies

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ABSTRACT

Diabetic nephropathy (DN), increasingly described within the broader clinical framework of diabetic kidney disease (DKD), represents a major microvascular complication of diabetes mellitus and a leading contributor to chronic kidney disease and end-stage kidney failure worldwide. Its pathogenesis involves complex interactions among chronic hyperglycaemia, haemodynamic abnormalities, oxidative stress, inflammatory mediators, mitochondrial dysfunction, endothelial injury, podocyte damage and progressive extracellular matrix accumulation. Historically, the understanding of DN has evolved from morphological descriptions of glomerulosclerosis to the identification of hyperfiltration, renin–angiotensin–aldosterone system activation and multiple intracellular signalling networks. This review examines the historical development and molecular basis of DN, emphasising advanced glycation end-products and receptor for advanced glycation end-products signalling, protein kinase C activation, polyol and hexosamine pathways, transforming growth factor-β/Smad signalling, nuclear factor-κB, mitogen-activated protein kinases, phosphatidylinositol-3-kinase/Akt/mTOR, AMP-activated protein kinase, Nrf2/Keap1, Wnt/β-catenin and NLRP3 inflammasome activation. Particular attention is given to podocyte dysfunction, glomerular endothelial abnormalities, tubular metabolic stress, epigenetic regulation and renal fibrosis. Contemporary therapeutic strategies, including renin–angiotensin system inhibitors, sodium–glucose cotransporter-2 inhibitors, glucagon-like peptide-1 receptor agonists and non-steroidal mineralocorticoid receptor antagonists, are evaluated alongside landmark clinical trials and emerging molecular interventions. The review also discusses integrated treatment approaches, biomarker-based risk stratification and future therapeutic directions. Understanding the convergence of metabolic, haemodynamic and inflammatory pathways is essential for developing individualized, evidence-based interventions capable of delaying renal disease progression and improving long-term cardiorenal outcomes.

Keywords: Diabetic kidney disease; diabetic nephropathy; AGE–RAGE signalling; glomerular hyperfiltration; podocytopathy; mitochondrial oxidative stress; TGF-β/Smad pathway; NLRP3 inflammasome; renal fibrogenesis; cardiorenal pharmacotherapy.

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Received 20 October 2026, Accepted 13 November 2026

Please cite this article as: Mehta., Molecular Mechanisms in the Pathogenesis of Diabetic Nephropathy: Historical Development, Intracellular Signalling Pathways, Molecular Targets and Contemporary Therapeutic Strategies. American Journal of Pharmacy & Health Research 2026.

INTRODUCTIONs

Diabetic nephropathy is a progressive renal complication associated with both type 1 and type 2 diabetes mellitus. It is characterized by structural and functional alterations involving the glomerular filtration barrier, renal microvasculature, mesangial compartment and tubular interstitium. Clinically, the condition may manifest as persistent albuminuria, declining glomerular filtration rate (GFR), hypertension and, in advanced cases, kidney failure.

The term diabetic kidney disease is increasingly preferred in clinical practice because not all individuals with diabetes and impaired renal function demonstrate classical histopathological features of diabetic glomerulosclerosis. Some patients develop a progressive reduction in estimated GFR without substantial albuminuria.

The pathogenesis of this condition cannot be attributed exclusively to hyperglycaemia. Rather, it represents a multifactorial pathological process involving:

- Chronic metabolic disturbances.
- Intraglomerular haemodynamic alterations
- Excessive generation of reactive oxygen species.
- Advanced glycation end-product accumulation.
- Activation of inflammatory signalling pathways.
- Podocyte and endothelial dysfunction.
- Mitochondrial and endoplasmic reticulum stress.
- Progressive extracellular matrix deposition.
- Epigenetic modifications and metabolic memory.

These interconnected mechanisms contribute to progressive nephron damage and irreversible renal fibrosis. Recent research has established that the molecular mechanisms underlying diabetic kidney disease provide opportunities for therapeutic intervention beyond conventional glucose-lowering treatment [1–4].

Objectives of the review

The principal objectives of this review are:

- To describe the historical development of diabetic nephropathy research.
- To examine the biochemical and molecular mechanisms responsible for renal injury.
- To analyse major intracellular signalling pathways involved in disease progression.
- To investigate the contribution of podocytes, mesangial cells, endothelial cells and tubular epithelial cells.

- To evaluate established pharmacological interventions and their molecular mechanisms.
- To discuss landmark clinical trials and therapeutic developments through November 2026.
- To identify emerging molecular targets and potential directions for precision nephrology.

HISTORICAL DEVELOPMENT OF DIABETIC NEPHROPATHY RESEARCH

The understanding of diabetic nephropathy has progressed through several important stages, from clinical observation and histopathological examination to molecular pharmacology and targeted cardiorenal protection.

Early pathological observations

During the nineteenth and early twentieth centuries, investigators identified characteristic renal abnormalities in individuals suffering from diabetes mellitus. The association between diabetes, proteinuria, glomerular lesions and progressive renal dysfunction gradually established diabetic nephropathy as a distinct pathological entity. The identification of glomerular basement membrane thickening, mesangial expansion and nodular glomerulosclerosis provided important pathological foundations.

Development of the hyperfiltration hypothesis

During the 1970s and 1980s, investigations demonstrated that early diabetes could produce increased renal blood flow, glomerular hyperfiltration and renal hypertrophy. Mogensen and colleagues subsequently proposed a staged model of diabetic renal disease in 1983, describing early hyperfunction, clinically silent structural alterations, incipient nephropathy and progressive overt renal disease [5]. This framework established the importance of early renal haemodynamic abnormalities in the pathogenesis of diabetic kidney injury.

Recognition of the renin–angiotensin system

The subsequent development of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) represented a major therapeutic advancement. Experimental and clinical investigations established that angiotensin II contributes to efferent arteriolar vasoconstriction, intraglomerular hypertension, oxidative stress and profibrotic signalling. The RENAAL and IDNT clinical trials subsequently demonstrated the importance of angiotensin receptor blockade in reducing renal disease progression among individuals with type 2 diabetes and nephropathy [6,7].

Metabolic and molecular mechanisms

During the 1990s and early 2000s, investigations increasingly focused on the biochemical consequences of chronic hyperglycaemia.

Important mechanisms included:

- Advanced glycation end-product formation.
- Protein kinase C activation.
- Polyol pathway activation.
- Hexosamine pathway activation.
- Reactive oxygen species generation.
- Transforming growth factor-β-mediated fibrosis.

The identification of these pathways helped explain how sustained hyperglycaemia produces cellular injury beyond its immediate metabolic effects.

Emergence of contemporary cardiorenal pharmacotherapy

The twenty-first century witnessed a major transition from conventional glycaemic management towards therapies that directly influence renal and cardiovascular outcomes.

Important developments included:

Period	Major Development	Scientific Significance
1983	Mogensen Classification	Staging of diabetic renal disease
1993	DCCT Findings	Importance of intensive glycaemic control
2001	RENAAL and IDNT Trials	Renal protection through angiotensin receptor blockade
2010	ADVANCE-ON Follow-up	Long-term implications of glycaemic management
2019	CREDENCE Trial	SGLT2 inhibition and kidney protection
2020	DAPA-CKD Trial	Kidney protection extending beyond diabetes
2020–2021	FIDELIO-DKD and FIGARO-DKD Trials	Non-steroidal mineralocorticoid receptor antagonism
2022	EMPA-KIDNEY Trial	Broad kidney protection with empagliflozin
2024	FLOW Trial	Semaglutide and clinically important kidney outcomes
2025–2026	Integrated Cardiorenal and Molecular Approaches	Combination therapy and investigation of new molecular targets

The recent therapeutic landscape is characterized by the integration of SGLT2 inhibitors, GLP-1 receptor agonists and non-steroidal mineralocorticoid receptor antagonists with conventional renin–angiotensin system inhibition [2,8–11].

Pathophysiology of diabetic nephropathy

The pathophysiology of diabetic nephropathy involves multiple interdependent processes. Persistent metabolic abnormalities initiate cellular stress, while haemodynamic changes increase the mechanical burden on the glomerular filtration barrier.

Chronic hyperglycaemia

Hyperglycaemia represents a central initiating factor in diabetic renal injury. Increased circulating glucose produces excessive intracellular glucose availability in susceptible renal cells, including mesangial cells, podocytes and proximal tubular epithelial cells.

This metabolic disturbance activates several biochemical pathways, resulting in:

- Increased intracellular glucose metabolism.
- Excessive generation of reactive oxygen species.
- Accumulation of advanced glycation end-products.
- Altered intracellular calcium homeostasis.
- Activation of inflammatory transcription factors.
- Increased expression of profibrotic mediators.

Hyperglycaemia also promotes mitochondrial dysfunction and abnormal cellular energy metabolism. The resulting oxidative and inflammatory environment contributes to glomerular basement membrane thickening, mesangial matrix expansion and tubular injury [1,3].

Glomerular hyperfiltration

Glomerular hyperfiltration is frequently observed during the early stages of diabetic kidney disease. Increased proximal tubular glucose and sodium reabsorption through sodium–glucose cotransporter 2 (SGLT2) reduces sodium chloride delivery to the macula densa. This alters tubuloglomerular feedback and promotes afferent arteriolar vasodilation. Simultaneously, activation of intrarenal renin–angiotensin signalling contributes to efferent arteriolar vasoconstriction. The combined effects increase intraglomerular pressure and filtration workload.

Pathophysiological sequence

- Chronic hyperglycaemia
- Increased proximal tubular glucose and sodium reabsorption
- Reduced macula densa sodium chloride delivery
- Altered tubuloglomerular feedback and afferent vasodilation
- Increased intraglomerular pressure and hyperfiltration
- Glomerular filtration barrier injury and albuminuria
- Progressive glomerulosclerosis and renal dysfunction

This mechanism provides an important pharmacological rationale for SGLT2 inhibitor treatment [2,12].

Glomerular filtration barrier injury

The glomerular filtration barrier consists of three principal components:

- Fenestrated glomerular endothelial cells.
- Glomerular basement membrane.
- Visceral epithelial cells known as podocytes.

Podocytes maintain filtration selectivity through specialized foot processes and slit diaphragm proteins, including nephrin and podocin. Hyperglycaemia, oxidative stress and inflammatory mediators disrupt podocyte cytoskeletal organization and slit diaphragm integrity. The resulting alterations increase glomerular permeability to albumin and other plasma proteins. Podocyte detachment, apoptosis and depletion are particularly important because mature podocytes possess limited regenerative capacity.

Mesangial cell dysfunction

Mesangial cells provide structural support to the glomerular capillary network. Chronic hyperglycaemia stimulates mesangial cell proliferation, hypertrophy and extracellular matrix synthesis.

Important mediators include:

- Transforming growth factor-β1 (TGF-β1).
- Fibronectin.
- Type IV collagen.
- Platelet-derived growth factor.
- Connective tissue growth factor.

Progressive mesangial matrix accumulation contributes to glomerulosclerosis and reduction in the effective filtration surface.

Tubulointerstitial injury

Although glomerular abnormalities are prominent, tubular and interstitial changes are major determinants of renal functional decline. Proximal tubular cells are exposed to increased glucose and filtered albumin. These conditions increase metabolic workload and promote mitochondrial stress. Tubular injury stimulates inflammatory cell recruitment and profibrotic signalling, resulting in interstitial matrix accumulation. Consequently, tubulointerstitial fibrosis represents an important pathological determinant of progressive kidney dysfunction [1,3].

MOLECULAR MECHANISMS INVOLVED IN DIABETIC NEPHROPATHY

Advanced glycation end-products and RAGE signalling

Advanced glycation end-products (AGEs) are heterogeneous compounds generated through non-enzymatic reactions between reducing sugars and proteins, lipids or nucleic acids. Chronic hyperglycaemia increases AGE formation and promotes their accumulation within renal tissues.

AGEs interact with the receptor for advanced glycation end-products (RAGE), which belongs to the immunoglobulin superfamily of cell-surface receptors.

RAGE activation stimulates intracellular signalling networks, particularly:

- Nuclear factor-κB (NF-κB).
- Mitogen-activated protein kinases (MAPKs).
- NADPH oxidase.
- Reactive oxygen species generation.

These events increase inflammatory cytokine production, endothelial dysfunction and extracellular matrix accumulation. The AGE–RAGE axis therefore contributes to both the initiation and progression of diabetic renal injury.

Molecular sequence

AGE accumulation → RAGE activation → NADPH oxidase stimulation → ROS generation → NF-κB activation → inflammatory cytokine expression → renal tissue injury.

Potential therapeutic approaches targeting AGE formation and RAGE signalling remain predominantly investigational. They have not yet replaced established kidney-protective therapies [1,3,13].

Protein kinase C signalling pathway

Protein kinase C (PKC) represents an important intracellular signalling system activated by metabolic abnormalities associated with diabetes. Increased intracellular glucose metabolism stimulates diacylglycerol formation, which activates conventional and novel PKC isoforms.

PKC activation produces several pathological effects:

- Increased vascular permeability.
- Altered renal blood flow.
- NADPH oxidase activation.
- Increased endothelin-1 production.
- Enhanced TGF-β expression.
- Abnormal extracellular matrix synthesis.

PKC-β has received particular attention because of its association with diabetic microvascular complications. Although selective PKC inhibition has demonstrated experimental promise, it has not become an established disease-modifying treatment for diabetic kidney disease.

Polyol pathway

The polyol pathway becomes increasingly active under conditions of excessive intracellular glucose availability. Aldose reductase catalyses the conversion of glucose into sorbitol using

NADPH as a reducing cofactor. Sorbitol is subsequently converted into fructose by sorbitol dehydrogenase.

This process contributes to:

- NADPH depletion.
- Reduced regeneration of reduced glutathione.
- Increased susceptibility to oxidative stress.
- Altered intracellular osmotic balance.
- Abnormal redox regulation.

The resulting oxidative imbalance may aggravate renal cellular damage.

Hexosamine biosynthetic pathway

Excess intracellular glucose also increases the availability of fructose-6-phosphate for the hexosamine biosynthetic pathway. The pathway ultimately generates uridine diphosphate N-acetylglucosamine (UDP-GlcNAc). UDP-GlcNAc serves as a substrate for O-linked N-acetylglucosamine modification of proteins. Abnormal O-GlcNAcylation alters the activity of transcription factors and signalling proteins. This can increase the expression of TGF-β, plasminogen activator inhibitor-1 and other profibrotic mediators.

Transforming growth factor-β/Smad signalling

The TGF-β/Smad pathway is one of the most important profibrotic signalling mechanisms in diabetic nephropathy. TGF-β1 binds to its type II receptor, which recruits and activates the type I receptor. The activated receptor phosphorylates Smad2 and Smad3. Phosphorylated Smad proteins form complexes with Smad4 and translocate into the nucleus. These complexes regulate the transcription of genes responsible for extracellular matrix synthesis.

Important downstream effects include:

- Increased collagen production.
- Fibronectin accumulation.
- Mesangial matrix expansion.
- Tubulointerstitial fibrosis.

TGF-β signalling also interacts with MAPK, PI3K/Akt and NF-κB pathways.

This cross-talk amplifies profibrotic activity and contributes to progressive renal structural damage [3,14].

Nuclear factor-κB signalling

NF-κB is a major transcriptional regulator of inflammation. Under resting conditions, NF-κB is retained in the cytoplasm through interaction with inhibitory IκB proteins. Inflammatory stimulation activates the IκB kinase complex, resulting in IκB phosphorylation and degradation.

NF-κB subsequently translocates into the nucleus and regulates genes encoding:

- Tumour necrosis factor-α.
- Interleukin-1β.
- Interleukin-6.
- Monocyte chemoattractant protein-1.
- Adhesion molecules.
- Proinflammatory enzymes.

In diabetic nephropathy, persistent NF-κB activation promotes leukocyte recruitment, glomerular inflammation and interstitial tissue damage.

NLRP3 inflammasome signalling

The NLRP3 inflammasome is an intracellular multiprotein complex involved in innate immune responses. Its activation generally requires two processes:

Priming: NF-κB-dependent stimulation increases NLRP3 and pro-IL-1β expression.

Activation: Cellular stress signals, including mitochondrial reactive oxygen species, potassium efflux and damage-associated molecular patterns, promote inflammasome assembly.

Activated NLRP3 recruits the adaptor protein ASC and procaspase-1.

Caspase-1 activation results in:

- Conversion of pro-IL-1β into mature IL-1β.
- Conversion of pro-IL-18 into mature IL-18.
- Gasdermin D cleavage.
- Pyroptotic inflammatory cell death.

This pathway contributes to renal inflammation and tissue injury.

NLRP3 inhibition is an emerging experimental therapeutic strategy, but routine clinical use for diabetic kidney disease is not currently established [4,15].

PI3K/Akt/mTOR signalling

The phosphatidylinositol-3-kinase/Akt/mTOR pathway regulates cellular growth, survival, metabolism and autophagy.

In diabetic renal tissue, abnormal activation of this pathway contributes to:

- Mesangial cell hypertrophy.
- Podocyte dysfunction.

- Abnormal protein synthesis.
- Altered autophagic activity.
- Cellular metabolic reprogramming.

Mechanistic target of rapamycin complex 1 (mTORC1) is particularly important in regulating protein synthesis and cellular growth. Excessive mTORC1 activity can suppress autophagy and contribute to podocyte injury. The relationship between PI3K/Akt/mTOR signalling and renal injury is cell-specific and context-dependent; therefore, indiscriminate inhibition may also interfere with physiological cellular repair.

AMP-activated protein kinase signalling

AMP-activated protein kinase (AMPK) is a major cellular energy sensor. It responds to changes in the intracellular AMP-to-ATP ratio and regulates metabolic adaptation.

AMPK activation promotes:

- Fatty acid oxidation.
- Mitochondrial homeostasis.
- Glucose metabolism regulation.
- Autophagy.
- Suppression of excessive mTORC1 activity.
- Improved cellular stress resistance.

Reduced AMPK activity has been associated with metabolic dysfunction in experimental diabetic nephropathy. Pharmacological agents such as metformin influence AMPK-related metabolic signalling, although their renal benefits should not be interpreted as proof of a direct AMPK-mediated disease-modifying effect in humans.

Nrf2/Keap1 antioxidant signalling

Nuclear factor erythroid 2-related factor 2 (Nrf2) is an important regulator of cellular antioxidant defence. Under basal conditions, Nrf2 is regulated by Kelch-like ECH-associated protein 1 (Keap1), which promotes its ubiquitination and degradation. Oxidative or electrophilic stress modifies this regulatory system and allows Nrf2 to accumulate and translocate into the nucleus.

Nrf2 binds antioxidant response elements and stimulates the expression of protective enzymes, including:

- Heme oxygenase-1.
- NAD(P)H quinone dehydrogenase 1.
- Glutathione-related enzymes.
- Other antioxidant defence proteins.

Impaired Nrf2 activity contributes to oxidative stress and cellular injury. Nrf2 activation remains an important area of investigation for renal cytoprotection [1,4].

Wnt/β-catenin signalling

Wnt/β-catenin signalling regulates cellular differentiation, proliferation and tissue development Under pathological conditions, excessive activation can contribute to renal fibrosis. Wnt ligands bind to Frizzled receptors and LRP5/6 co-receptors, inhibiting the β-catenin destruction complex. Accumulated β-catenin translocates into the nucleus and regulates target gene transcription.

In diabetic renal disease, abnormal Wnt/β-catenin signalling is associated with:

- Tubular epithelial dysfunction.
- Fibroblast activation.
- Extracellular matrix accumulation.
- Abnormal cellular differentiation.
- Renal fibrosis.

The pathway represents a potential target for future antifibrotic drug development [14].

JAK/STAT signalling

The Janus kinase/signal transducer and activator of transcription pathway regulates inflammatory and growth-factor-mediated cellular responses. Cytokine binding activates receptor-associated JAK proteins, which phosphorylate STAT transcription factors. Activated STAT proteins dimerise and enter the nucleus, where they regulate gene expression. In diabetic kidney disease, JAK/STAT signalling contributes to inflammatory responses, cellular proliferation and fibrosis.

JAK1/STAT3 and related signalling components have been investigated as potential therapeutic targets, but their inhibition requires careful consideration of systemic immune effects.

Mitochondrial dysfunction and oxidative stress

Mitochondria are essential for cellular ATP generation and metabolic regulation. Chronic hyperglycaemia increases mitochondrial substrate availability and alters electron transport chain activity.

Excessive mitochondrial reactive oxygen species generation contributes to:

- Lipid peroxidation.
- Protein oxidation.
- Mitochondrial DNA damage.
- Impaired oxidative phosphorylation.
- Apoptosis.
- Abnormal cellular energy metabolism.

Mitochondrial dynamics are also affected through alterations in fission and fusion proteins. The interaction between oxidative stress, mitochondrial dysfunction and inflammatory signalling establishes a self-amplifying cycle of renal injury [1,3].

Epigenetic modifications and metabolic memory

Metabolic memory refers to the persistence of diabetic complications despite subsequent improvement in glycaemic control.

This phenomenon is associated with sustained molecular changes involving:

- DNA methylation.
- Histone modifications.
- Non-coding RNAs.
- MicroRNA expression.
- Long non-coding RNAs.
- Chromatin remodelling.

Epigenetic changes can maintain abnormal transcriptional activity involving inflammatory and fibrotic genes. MicroRNAs such as miR-21, miR-29 and miR-192 have been investigated in relation to renal fibrosis and diabetic kidney injury. However, their expression and biological effects may vary according to tissue, disease stage and experimental conditions. Epigenetic regulation represents a promising field for biomarker development and targeted intervention, although clinical translation remains limited [3,4].

MAJOR CELLULAR AND MOLECULAR TARGETS IN DIABETIC NEPHROPATHY

The molecular mechanisms described above operate through interactions among several renal cell populations. Understanding these interactions is important for identifying therapeutic targets.

Renal Cell Population	Major Pathological Alterations	Important Molecular Mediators
Podocytes	Foot-process effacement, apoptosis and detachment	Nephrin, podocin, TRPC5/6, PI3K/Akt
Mesangial Cells	Hypertrophy and matrix expansion	TGF-β1, Smad2/3, PKC
Endothelial Cells	Endothelial dysfunction and glycocalyx injury	eNOS, VEGF, NOX
Proximal Tubular Cells	Metabolic overload and mitochondrial injury	SGLT2, AMPK, mTOR
Macrophages	Inflammatory activation and cytokine release	NF-κB, NLRP3, JAK/STAT
Renal Fibroblasts	Myofibroblast activation and matrix deposition	TGF-β/Smad, Wnt/β-catenin

Podocyte injury and slit diaphragm dysfunction

Podocytes are highly specialized epithelial cells that maintain the integrity of the glomerular filtration barrier. Hyperglycaemia and angiotensin II can alter intracellular calcium regulation and activate transient receptor potential channels, particularly TRPC5 and TRPC6. Abnormal calcium signalling disrupts the actin cytoskeleton and contributes to podocyte foot-process effacement. Reduced expression or altered localization of nephrin and podocin further compromises filtration selectivity. Recent mechanistic investigations have also identified interactions among insulin signalling, cholesterol metabolism, mitochondrial function and podocyte senescence [4].

Endothelial dysfunction

Glomerular endothelial cells regulate vascular permeability and maintain appropriate filtration dynamics. Oxidative stress reduces nitric oxide bioavailability and promotes endothelial dysfunction. Alterations in endothelial nitric oxide synthase (eNOS), vascular endothelial growth factor (VEGF) signalling and endothelial glycocalyx integrity contribute to glomerular barrier abnormalities. The imbalance between angiogenic and antiangiogenic signals may further aggravate renal microvascular injury.

Macrophage infiltration and immune dysregulation

Persistent metabolic stress promotes the recruitment of monocytes and macrophages into renal tissue. These immune cells release cytokines, chemokines and reactive oxygen species. The traditional M1/M2 macrophage classification provides a simplified description of inflammatory and reparative phenotypes; actual macrophage populations demonstrate greater biological heterogeneity. In diabetic nephropathy, dysregulated macrophage activity contributes to chronic inflammation, defective tissue repair and fibrosis.

Tubular epithelial cell injury and maladaptive repair

Proximal tubular cells possess high metabolic requirements and are particularly vulnerable to mitochondrial dysfunction. Persistent glucose overload, increased albumin uptake and lipid accumulation can impair cellular energy metabolism. Injured tubular epithelial cells release inflammatory and profibrotic mediators, promoting interstitial macrophage recruitment and fibroblast activation. Maladaptive epithelial repair contributes to chronic interstitial fibrosis and nephron loss.

INTEGRATED MOLECULAR SIGNALLING NETWORKS

Diabetic nephropathy should not be understood as a collection of independent molecular abnormalities. Instead, the disease develops through interconnected signalling networks.

Central molecular network of diabetic kidney disease

- Chronic hyperglycaemia and metabolic overload
- AGE–RAGE
- Oxidative stress
- PKC / polyol
- Metabolic dysregulation
- RAAS / MAPK
- Haemodynamic stress
- NF-κB / NLRP3
- Inflammation
- TGF-β / Smad
- Fibrogenesis
- mTOR / AMPK
- Cellular metabolism
- Podocyte, endothelial and tubular injury
- Glomerulosclerosis, tubulointerstitial fibrosis and progressive nephron loss

Figure 1: Conceptual representation of major interacting pathways in diabetic kidney disease. This is a schematic synthesis of published mechanistic research, rather than a quantitative pathway map.

PHARMACOLOGICAL MANAGEMENT OF DIABETIC NEPHROPATHY

The management of diabetic kidney disease has undergone substantial development. Contemporary treatment focuses on reducing albuminuria, controlling blood pressure, optimizing glycaemic status, limiting intraglomerular pressure and preventing cardiovascular complications. The therapeutic objective is not merely to reduce blood glucose but to preserve renal function and reduce the risk of kidney failure.

Renin–angiotensin–aldosterone system inhibitors

The renin–angiotensin–aldosterone system (RAAS) is a central regulator of renal haemodynamics, sodium balance and blood pressure. In diabetes, increased intrarenal RAAS activity contributes to glomerular hypertension and renal inflammation.

Two principal pharmacological classes are used.

Angiotensin-converting enzyme inhibitors

Examples:

- Ramipril.

- Enalapril.
- Lisinopril.
- Perindopril.

Mechanism of action:

ACE inhibitors reduce the conversion of angiotensin I into angiotensin II.

This produces:

- Reduced angiotensin II formation.
- Reduced efferent arteriolar vasoconstriction.
- Reduced intraglomerular pressure.
- Reduced aldosterone secretion.
- Decreased albuminuria.
- Reduced profibrotic and inflammatory signalling.

Angiotensin receptor blockers

Examples:

- Losartan.
- Telmisartan.
- Irbesartan.
- Valsartan.

ARBs selectively inhibit angiotensin II type 1 receptors. This reduces the haemodynamic and cellular effects of angiotensin II. The RENAAL and IDNT trials provided important evidence supporting ARB therapy in type 2 diabetic nephropathy [6,7]. Established standard of care ACE inhibitors or ARBs are recommended for patients with diabetes, hypertension and moderately or severely increased albuminuria. Treatment should generally use the maximum tolerated approved dose. ACE inhibitors and ARBs should not routinely be combined because dual blockade increases adverse effects, particularly hyperkalaemia and acute kidney injury [8].

Sodium–glucose cotransporter-2 inhibitors

SGLT2 inhibitors have fundamentally changed the management of diabetic kidney disease. The proximal renal tubule expresses SGLT2, which reabsorbs a substantial proportion of filtered glucose and sodium. Pharmacological inhibition reduces glucose and sodium reabsorption.

Examples:

- Empagliflozin.
- Dapagliflozin.
- Canagliflozin.

Mechanisms of renoprotection

- Reduced proximal tubular glucose reabsorption.
- Restoration of tubuloglomerular feedback.
- Reduction of intraglomerular pressure.
- Reduction in albuminuria.
- Modulation of renal oxygen consumption.
- Improvement in metabolic efficiency.
- Reduction in inflammatory and oxidative stress signalling.

SGLT2 inhibitors also produce beneficial effects on body weight, blood pressure and cardiovascular haemodynamics. Importantly, their kidney-protective effects are not exclusively dependent on reductions in HbA1c.

Major clinical trials

Trial	Drug	Major Contribution
CREDENCE (2019)	Canagliflozin	Demonstrated renal and cardiovascular benefits in patients with type 2 diabetes and albuminuric CKD.
DAPA-CKD (2020)	Dapagliflozin	Demonstrated protection against CKD progression in populations with and without diabetes.
EMPA-KIDNEY (2023)	Empagliflozin	Extended evidence of kidney protection across a broad CKD population.

These studies established SGLT2 inhibitors as disease-modifying therapies rather than simply glucose-lowering agents [9–11].

Non-steroidal mineralocorticoid receptor antagonists

Mineralocorticoid receptor activation contributes to inflammation, oxidative stress and fibrosis. Finerenone is a selective non-steroidal mineralocorticoid receptor antagonist that blocks pathological mineralocorticoid receptor signalling.

Its pharmacological effects include:

- Reduced inflammatory gene expression.
- Reduced profibrotic signalling.
- Modulation of oxidative stress.
- Reduction in albuminuria.
- Improvement in cardiorenal outcomes.

The FIDELIO-DKD and FIGARO-DKD trials demonstrated clinically important kidney and cardiovascular benefits in patients with type 2 diabetes and chronic kidney disease receiving

background standard treatment [12,13]. The pooled FIDELITY analysis further supported its cardiorenal benefits.

Evidence-based combination option

Finerenone may be added to a maximally tolerated ACE inhibitor or ARB, particularly when albuminuria persists and the patient meets eligibility criteria. KDIGO 2024 supports consideration of a non-steroidal mineralocorticoid receptor antagonist in appropriate patients with type 2 diabetes, CKD, albuminuria and normal serum potassium [8].

Glucagon-like peptide-1 receptor agonist

GLP-1 receptor agonists improve glycaemic regulation and provide additional metabolic and cardiovascular benefits.

Examples include:

- Semaglutide.
- Liraglutide.
- Dulaglutide.

Mechanisms of action include:

- Glucose-dependent stimulation of insulin secretion.
- Suppression of inappropriate glucagon secretion.
- Delayed gastric emptying, particularly during initial treatment.
- Reduction in body weight.
- Improvement in metabolic regulation.
- Modulation of inflammatory and oxidative stress pathways.

FLOW trial

The FLOW trial represented an important development in the evidence for GLP-1 receptor agonists in diabetic kidney disease. Semaglutide demonstrated a reduction in the primary composite kidney and cardiovascular death outcome among individuals with type 2 diabetes and CKD.

The findings expanded the role of GLP-1 receptor agonists from predominantly metabolic and cardiovascular management to clinically meaningful kidney protection [14].

Conventional glucose-lowering agents

Metformin

Metformin remains an important glucose-lowering treatment in type 2 diabetes when renal function permits. Its principal mechanism involves suppression of hepatic glucose production and improvement in insulin sensitivity. AMPK-related signalling is one proposed component of

its metabolic effects. Metformin should not be initiated or continued without appropriate renal-function assessment. It is contraindicated when eGFR is below 30 mL/min/1.73 m², and dose adjustment and closer monitoring are required in appropriate patients with reduced eGFR.

Insulin

Insulin is essential in type 1 diabetes and may be required in advanced type 2 diabetes. It reduces hyperglycaemia by promoting glucose uptake and suppressing hepatic glucose production. As renal function declines, insulin clearance may decrease, increasing the risk of hypoglycaemia. Therefore, dose reassessment is important.

DPP-4 inhibitors

Examples include sitagliptin, linagliptin and saxagliptin. These drugs improve endogenous incretin activity by inhibiting dipeptidyl peptidase-4. They may be useful for glycaemic management in selected patients, but they should not be considered substitutes for SGLT2 inhibitors, GLP-1 receptor agonists or finerenone when kidney protection is the treatment objective.

Blood pressure management

Hypertension accelerates diabetic kidney disease by increasing glomerular pressure and vascular injury.

The treatment approach includes:

- ACE inhibitors or ARBs when indicated.
- Calcium channel blockers.
- Thiazide-like or loop diuretics according to renal function and volume status.
- Dietary sodium reduction.
- Regular blood pressure monitoring.

An individualised blood pressure target is important, with a target below 130/80 mmHg commonly considered in patients with diabetes when safely attainable.

Lipid management

Dyslipidaemia contributes to cardiovascular risk and may aggravate renal lipotoxicity.

Statins are recommended according to cardiovascular risk, age and CKD status.

Examples include:

- Atorvastatin.
- Rosuvastatin.
- Simvastatin.

Their primary established clinical role in this population is cardiovascular risk reduction rather than reversal of established glomerular fibrosis.

CONTEMPORARY TREATMENT PROTOCOLS AND CLINICAL DECISION-MAKING

The following is an evidence-based educational framework synthesized from the ADA Standards of Care 2026 and KDIGO recommendations. It is not an individual prescription.

Initial evaluation Every patient with diabetes should undergo appropriate renal risk assessment.

Investigation	Clinical Importance
Urinary Albumin-to-Creatinine Ratio (UACR)	Detects albuminuria
Estimated Glomerular Filtration Rate (eGFR)	Assesses kidney function
Serum Creatinine	Evaluates renal filtration
Serum Potassium	Guides RAAS inhibitor and finerenone safety
HbA1c	Evaluates glycaemic control
Blood Pressure	Assesses haemodynamic risk
Lipid Profile	Evaluates cardiovascular risk
Urinalysis	Helps identify alternative renal pathology

In type 2 diabetes, kidney screening should begin at diagnosis. In type 1 diabetes, screening generally begins after five years of disease duration.

An abnormal UACR should generally be confirmed because albumin excretion varies with exercise, infection, fever, menstruation and other temporary conditions [16].

Risk classification

The following table presents the KDIGO GFR and albuminuria framework.

Category	eGFR (mL/min/1.73 m²)	Interpretation
G1	≥90	Normal or high
G2	60–89	Mildly decreased
G3a	45–59	Mildly to moderately decreased
G3b	30–44	Moderately to severely decreased
G4	15–29	Severely decreased
G5	Less than 15	Kidney failure

Albuminuria classification:

Category	UACR (mg/g)	Interpretation
A1	Less than 30	Normal to mildly increased
A2	30–300	Moderately increased
A3	Greater than 300	Severely increased

Both classifications should be interpreted together to estimate renal and cardiovascular risk.

Integrated pharmacological treatment framework

Step 1 — Establish the diagnosis and baseline risk

- Measure UACR and eGFR.
- Assess blood pressure and HbA1c.
- Identify cardiovascular disease and other CKD causes.

Step 2 — Optimize foundational management

- Individualised glycaemic control.
- Blood pressure control.
- Dietary and lifestyle interventions.
- ACE inhibitor or ARB when indicated.

Step 3 — Introduce kidney-protective treatment

- SGLT2 inhibitor for eligible patients with type 2 diabetes and CKD.
- GLP-1 receptor agonist with demonstrated kidney benefit when indicated.
- Consider finerenone for persistent albuminuria with appropriate eGFR and potassium.

Step 4 — Monitor safety and treatment response

- Repeat eGFR and UACR.
- Monitor serum potassium.
- Assess volume status and blood pressure.
- Review hypoglycaemia and other adverse effects.

Step 5 — Manage advanced disease

- Nephrology referral when appropriate.
- Assess complications of advanced CKD.
- Plan kidney replacement therapy when indicated.

Important pharmacological considerations

Drug Class	Commonly Used Regimen	Important Precautions
Empagliflozin	10 mg once daily	Volume depletion, genital infections and ketoacidosis risk
Dapagliflozin	10 mg once daily	Volume status, ketoacidosis risk and renal eligibility
Finerenone	10 or 20 mg once daily according to eGFR and potassium levels	Hyperkalaemia; monitor serum potassium
Semaglutide	Gradual dose escalation; kidney-outcome trial used 1 mg weekly	Gastrointestinal effects, dehydration and gallbladder events
Metformin	Individualised oral regimen	Renal dose assessment and lactic acidosis precautions
Ramipril	Individualised titration	Hyperkalaemia, hypotension and changes in creatinine
Losartan	Individualised titration	Hyperkalaemia, hypotension and changes in creatinine

The doses above are representative adult regimens, not universal treatment instructions. Actual selection, initiation and adjustment depend on the product label, eGFR, potassium concentration, comorbidities, concomitant medicines and patient tolerance.

Monitoring after treatment initiation

Particular attention should be given to:

- Serum creatinine and potassium after initiating or increasing ACE inhibitor or ARB therapy.
- Potassium and renal function after finerenone initiation.
- Volume status and blood pressure during SGLT2 inhibitor treatment.
- Symptoms of ketoacidosis during periods of acute illness or prolonged fasting.
- HbA1c and hypoglycaemia risk during glucose-lowering treatment.
- UACR and eGFR trends over time.

An initial reversible eGFR reduction may occur after SGLT2 inhibitor initiation or RAAS blockade. This should be interpreted in the context of the overall clinical condition rather than automatically considered treatment failure.

The 2024 KDIGO guideline recommends checking blood pressure, serum creatinine and potassium within 2–4 weeks of starting or increasing a RAAS inhibitor, with timing individualised to risk [8].

EMERGING THERAPEUTIC TARGETS AND FUTURE PHARMACOLOGICAL INTERVENTIONS

Despite substantial progress in the management of diabetic nephropathy, current therapies do not completely reverse established glomerulosclerosis or interstitial fibrosis. Consequently, research is increasingly directed towards molecular interventions that target inflammation, oxidative stress, mitochondrial dysfunction, cellular senescence and maladaptive tissue repair.

Endothelin receptor antagonists

Endothelin-1 is a potent vasoconstrictor peptide involved in renal vascular regulation.

Excessive endothelin signalling contributes to:

- Glomerular haemodynamic abnormalities.
- Podocyte injury.
- Inflammatory activation.
- Renal fibrosis.
- Increased albuminuria.

Selective endothelin-A receptor antagonists are being investigated as additional treatments for proteinuric CKD. Atrasentan has demonstrated albuminuria-lowering and kidney-protective potential in clinical research. However, fluid retention and heart failure risk require careful consideration. Combination approaches involving endothelin-A receptor blockade and SGLT2 inhibition represent an important area of investigation.

Aldosterone synthase inhibition

Aldosterone promotes sodium retention, potassium excretion, inflammation and fibrotic signalling. Aldosterone synthase inhibitors target the enzyme responsible for aldosterone biosynthesis. Baxdrostat and other investigational agents have generated interest because they may reduce excessive aldosterone production. Their potential role in diabetic kidney disease requires further outcome-based clinical evaluation.

NLRP3 inflammasome inhibition

NLRP3 inhibition is being investigated as an approach to reducing inflammatory injury.

Potential pharmacological strategies include:

- Direct NLRP3 inhibitors.
- Caspase-1 inhibitors.
- IL-1β pathway inhibition.
- Modulation of mitochondrial oxidative stress.

These approaches may interrupt the inflammatory amplification cycle associated with renal injury. However, their clinical efficacy and safety in diabetic kidney disease remain to be established.

Targeting mitochondrial dysfunction

Mitochondrial dysfunction is increasingly recognized as an important contributor to diabetic renal injury.

Investigational strategies include:

- Mitochondria-targeted antioxidants.
- Modulation of mitochondrial fission and fusion.
- Improvement of mitochondrial biogenesis.
- Regulation of NAD+/sirtuin signalling.
- Restoration of mitochondrial autophagy.

These approaches may help preserve tubular and podocyte metabolic function.

Ferroptosis inhibition

Ferroptosis is an iron-dependent form of regulated cell death characterized by excessive lipid peroxidation.

It is associated with disturbances in:

- Glutathione metabolism.
- Glutathione peroxidase 4 (GPX4).
- Iron homeostasis.
- Lipid oxidation.
- Mitochondrial and cellular redox regulation.

Experimental studies suggest that ferroptotic injury may contribute to renal tubular damage in diabetes. Ferrostatin-related compounds and other ferroptosis-modulating approaches are being investigated, but no ferroptosis inhibitor is currently an established treatment for diabetic nephropathy.

Epigenetic therapeutics

Epigenetic modulation offers the possibility of influencing persistent pathological gene expression without directly changing the DNA sequence.

Potential targets include:

- Histone deacetylases.
- Histone methyltransferases.
- DNA methyltransferases.
- Bromodomain-containing proteins.
- MicroRNAs.
- Long non-coding RNAs.

The challenge is achieving selective modulation of disease-associated gene expression without disrupting normal cellular functions.

RNA-based therapeutic approaches

MicroRNAs and long non-coding RNAs regulate gene expression at multiple levels. RNA-based therapeutic strategies may potentially regulate:

- TGF-β expression.
- Collagen synthesis.
- Inflammatory cytokine production.
- Podocyte survival.
- Fibroblast activation.

Antisense oligonucleotides and small interfering RNA approaches offer experimental opportunities for molecularly targeted treatment. Their translation into clinical nephrology will require improved delivery systems, renal tissue specificity and long-term safety evaluation.

Complement system modulation

The complement system participates in innate immunity and tissue injury. Complement activation may amplify inflammatory responses in diabetic renal tissue. Investigational approaches targeting complement components and regulatory proteins may provide future opportunities for patients with selected inflammatory kidney phenotypes.

Precision medicine and multi-omics approaches

Modern molecular research increasingly integrates multiple analytical technologies.

These include:

- Genomics.
- Transcriptomics.
- Proteomics.
- Metabolomics.
- Epigenomics.
- Single-cell RNA sequencing.
- Spatial transcriptomics.

These approaches allow researchers to investigate molecular changes within specific renal cell populations. Single-cell and spatial technologies are particularly valuable because diabetic kidney disease involves heterogeneous responses among podocytes, endothelial cells, tubular cells and immune populations. The integration of molecular biomarkers with clinical parameters may eventually enable more precise prediction of disease progression and therapeutic response.

RECENT SCIENTIFIC DEVELOPMENTS: 2024–2026

Research published during 2024–2026 has strengthened the understanding of diabetic kidney disease as a complex interaction between metabolic stress, inflammatory signalling, cellular dysfunction and renal fibrosis.

Molecular mechanisms and therapeutic convergence

Sun and colleagues published a review in 2024 examining molecular mechanisms associated with diabetic nephropathy, including inflammatory responses, oxidative stress, cellular injury, autophagy and epigenetic regulation [3]. Ansari and colleagues examined inflammatory and fibrotic mechanisms, highlighting NF-κB, JAK/STAT, NLRP3, TGF-β/Smad and Wnt/β-catenin signalling as important areas of investigation [15].

Integrated molecular and clinical understanding

Martinez Leon, Hilburg and Susztak published an important review in Nature Reviews Endocrinology in 2026, describing the convergence of glomerular hyperfiltration, podocyte injury, tubular dysfunction, inflammation and fibrosis. The review also discusses established therapies and emerging strategies, including combination approaches and targeted anti-inflammatory interventions [2].

Updated pharmacological recommendations

The American Diabetes Association's 2026 Standards of Care reinforce the importance of SGLT2 inhibitors and GLP-1 receptor agonists with demonstrated kidney benefits in patients with type 2 diabetes and CKD. The recommendations also support non-steroidal mineralocorticoid receptor antagonists in appropriately selected patients with albuminuric CKD [16].

New directions in cellular injury research

Research into pyroptosis, ferroptosis, cuproptosis and other forms of regulated cell death has expanded the molecular understanding of diabetic complications.These pathways provide additional explanations for cellular injury associated with oxidative stress, inflammatory signalling and metabolic disturbances [17].

Major therapeutic developments

Established clinical evidence

Clinical use

- ACE inhibitors and ARBs.
- SGLT2 inhibitors.
- Finerenone.
- GLP-1 receptor agonists with demonstrated kidney benefit.
- Individualised glycaemic and blood pressure management.

Emerging therapeutic research Under investigation

- NLRP3 inflammasome inhibition.
- Mitochondrial protection.
- Ferroptosis modulation.
- Epigenetic interventions.
- RNA-based therapeutics.
- Complement modulation.
- Endothelin and aldosterone pathway combinations.

COMPARATIVE ANALYSIS OF MAJOR CLINICAL TRIALS

Large-scale clinical trials have provided the strongest evidence for contemporary kidney-protective pharmacotherapy.

Trial	Publication	Intervention	Principal Scientific Contribution
DCCT	1993	Intensive insulin therapy	Established the importance of improved glycaemic control in type 1 diabetes.
RENAAL	2001	Losartan	Demonstrated renal protection in type 2 diabetic nephropathy.
IDNT	2001	Irbesartan	Established renal benefits of ARB therapy.
CREDENCE	2019	Canagliflozin	Demonstrated reduced kidney and cardiovascular risk.
DAPA-CKD	2020	Dapagliflozin	Established kidney protection in CKD with or without diabetes.
FIDELIO-DKD	2020	Finerenone	Demonstrated reduced kidney disease progression.
FIGARO-DKD	2021	Finerenone	Demonstrated cardiovascular benefit in a broader CKD population.
EMPA-KIDNEY	2023	Empagliflozin	Expanded evidence for kidney protection across CKD populations.
FLOW	2024	Semaglutide	Demonstrated clinically important kidney and cardiovascular outcome benefits.

The clinical importance of these studies lies in their demonstration that kidney protection is achievable through multiple complementary pharmacological mechanisms. The progression from glucose-centred therapy towards integrated cardiorenal protection represents one of the most significant developments in modern pharmacotherapy [2,8–14,16].

DISCUSSION

Diabetic nephropathy is a complex metabolic and vascular disorder involving multiple molecular pathways. Its progression reflects the interaction of chronic hyperglycaemia, intraglomerular hypertension, oxidative stress, inflammatory signalling and extracellular matrix accumulation. The classical explanation of diabetic nephropathy focused predominantly on hyperglycaemia and glomerular haemodynamic abnormalities. However, contemporary research has established that this explanation is incomplete.

AGE–RAGE signalling, PKC activation, TGF-β/Smad signalling, NF-κB activation and mitochondrial dysfunction provide important mechanistic explanations for the development of renal injury. An important observation is the interaction between oxidative stress and inflammation. Excessive ROS production stimulates inflammatory transcription factors, while inflammatory cytokines further aggravate mitochondrial dysfunction. This establishes a self-perpetuating cycle of cellular injury. Similarly, TGF-β-mediated extracellular matrix

accumulation contributes to progressive glomerulosclerosis and interstitial fibrosis. Once substantial fibrosis develops, restoration of normal renal architecture becomes difficult.

The development of SGLT2 inhibitors has changed the pharmacological approach to diabetic kidney disease. Their kidney-protective activity involves haemodynamic and metabolic effects that extend beyond glucose lowering.

Finerenone provides an additional mechanism of protection by modulating mineralocorticoid receptor-mediated inflammation and fibrosis. GLP-1 receptor agonists provide further metabolic and cardiovascular advantages, with semaglutide now supported by dedicated kidney-outcome evidence. These interventions should be considered complementary rather than interchangeable.

An important therapeutic principle is that treatment should address multiple pathological mechanisms simultaneously. For example, RAAS inhibition reduces intraglomerular pressure, SGLT2 inhibition modifies tubuloglomerular feedback and finerenone attenuates pathological mineralocorticoid receptor signalling. Nevertheless, the effectiveness of combination treatment must be balanced against the risk of hyperkalaemia, hypotension, volume depletion and other adverse effects. Emerging investigations into NLRP3, mitochondrial dysfunction, ferroptosis and epigenetic modifications may provide further therapeutic opportunities. However, mechanistic plausibility and positive experimental findings should not be interpreted as proof of clinical efficacy. The future of diabetic nephropathy management will probably depend on the integration of established pharmacological interventions with molecular biomarkers, personalised risk assessment and targeted therapies.

RESEARCH GAPS AND FUTURE PERSPECTIVES

Despite considerable progress, several important scientific questions remain unresolved.

Reversibility of established renal fibrosis

Current kidney-protective treatments primarily delay disease progression. More research is required to identify interventions capable of reversing established fibrotic changes.

Identification of early biomarkers

Albuminuria and eGFR remain central clinical markers, but they may not adequately identify all early molecular abnormalities.

Emerging biomarkers include:

- Kidney injury molecule-1 (KIM-1).
- Neutrophil gelatinase-associated lipocalin (NGAL).
- Urinary epidermal growth factor.
- Inflammatory cytokines.

- Selected circulating and urinary microRNAs.

Their routine clinical utility requires further validation.

Understanding non-albuminuric diabetic kidney disease

Not all individuals with diabetes and CKD demonstrate persistent albuminuria. Further research is required to understand the molecular mechanisms responsible for non-albuminuric renal function decline.

Development of cell-specific therapies

The same signalling pathway may produce different effects in different renal cell populations. Therefore, therapies targeting a specific cellular compartment may provide greater efficacy and fewer systemic adverse effects.

Long-term combination pharmacotherapy

Further studies are required to determine the optimal sequencing, combination and long-term safety of RAAS inhibitors, SGLT2 inhibitors, finerenone and GLP-1 receptor agonists.

Translational research in Indian populations

India has a substantial burden of diabetes mellitus and related cardiovascular and renal complications.

Research involving Indian populations should investigate:

- Genetic and environmental risk factors.
- Diabetes duration and glycaemic exposure.
- Dietary and metabolic influences.
- Socioeconomic barriers to early diagnosis.
- Access to kidney-protective medicines.
- Long-term treatment adherence.
- Cost-effectiveness of combination pharmacotherapy.

Such studies may help develop treatment approaches that are scientifically appropriate and economically accessible.

Limitations of the review

This article is a narrative scientific review rather than a systematic review or meta-analysis.

It synthesizes selected historical studies, molecular investigations, clinical trials and contemporary recommendations. It does not claim exhaustive retrieval of all published literature.

The interpretation of experimental molecular pathways is subject to limitations because some findings are derived from animal models, cultured renal cells or preclinical investigations.

Furthermore, emerging therapeutic targets should be distinguished from interventions with established clinical kidney-outcome evidence. The discussion of treatment protocols is educational and does not replace individualised clinical assessment or prescribing decisions.

CONCLUSION

Diabetic nephropathy represents a multifactorial renal disorder involving complex interactions among metabolic disturbances, haemodynamic abnormalities, oxidative stress, inflammatory responses and profibrotic signalling networks. The historical development of diabetic nephropathy research has transformed the understanding of this condition from a predominantly morphological disease into a molecularly regulated pathological process involving multiple renal cell populations. AGE–RAGE, PKC, TGF-β/Smad, NF-κB, NLRP3, PI3K/Akt/mTOR, AMPK and Nrf2 pathways represent important molecular mechanisms involved in disease progression. Their interactions contribute to podocyte injury, mesangial expansion, endothelial dysfunction, tubular metabolic stress and progressive extracellular matrix deposition.

The introduction of RAAS inhibitors, SGLT2 inhibitors, non-steroidal mineralocorticoid receptor antagonists and GLP-1 receptor agonists has substantially expanded the therapeutic possibilities for patients with diabetic kidney disease. The evidence generated through CREDENCE, DAPA-CKD, EMPA-KIDNEY, FIDELIO-DKD, FIGARO-DKD and FLOW has established the importance of comprehensive cardiorenal protection.

Future research should concentrate on developing interventions that target mitochondrial dysfunction, inflammatory signalling, cellular senescence, epigenetic regulation and renal fibrosis. Integration of multi-omics technologies, molecular biomarkers and precision pharmacotherapy may further improve early diagnosis and treatment selection.

Ultimately, the management of diabetic nephropathy requires a transition from isolated glucose control towards comprehensive, mechanism-oriented and individualised renal protection. Continued translational research will be essential for identifying therapeutic strategies capable of preserving renal architecture, maintaining kidney function and reducing the global burden of diabetes-associated kidney disease.

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