REVIEW ARTICLE

UNRAVELLING DIABETIC NEPHROPATHY: PATHOPHYSIOLOGY, DIAGNOSIS, AND THERAPEUTIC STRATEGIES

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Abstract:

Diabetic nephropathy (DN) is a leading cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD) worldwide, representing a major microvascular complication of diabetes mellitus. Despite advances in understanding the disease, the global burden of DN continues to rise, underscoring the need for comprehensive insight into its underlying mechanisms and effective management approaches. This review explores the complex pathophysiology of DN, including hyperglycemia-induced oxidative stress, inflammation, hemodynamic changes, and fibrosis, which collectively contribute to progressive renal damage. Diagnostic strategies are discussed with a focus on traditional markers such as albuminuria and estimated glomerular filtration rate (eGFR), as well as emerging biomarkers that may enable earlier and more precise detection. In terms of treatment, current standard therapies including renin–angiotensin–aldosterone system (RAAS) inhibitors are evaluated alongside newer agents such as SGLT2 inhibitors, GLP-1 receptor agonists, and endothelin receptor antagonists. The review also highlights ongoing research into novel therapeutic targets and the potential for personalized medicine in managing DN. A better understanding of the multifactorial nature of diabetic nephropathy is essential for improving patient outcomes and reducing the global impact of diabetic kidney disease.

Keyword: Diabetic Nephropathy, Chronic Kidney Disease, Oxidative Stress, Biomarkers, Personalized Medicine.

Introduction:

Diabetes mellitus (DM) stands as the primary cause of chronic kidney disease in developing countries and continues to rise as a global contributor to morbidity and mortality. Both type 1 and type 2 diabetes are involved, but type 2 diabetes plays a more significant role due to its higher prevalence and associated complications. Among the various complications, diabetic nephropathy (DN) has emerged as the leading cause of end-stage renal disease (ESRD) and cardiovascular-related deaths. Typically, DN develops after several years of diabetes progression.[1][2]

The progression and clinical course of diabetic nephropathy differ depending on the type of diabetes and the presence of microalbuminuria defined as urinary albumin excretion between 30 and 300 mg/day. If left unmanaged, around 80% of individuals with type 1 diabetes and microalbuminuria may progress to overt nephropathy, characterized by daily albumin excretion exceeding 300 mg. In contrast, only about 20–40% of type 2 diabetic patients will develop nephropathy over a 15-year period. Furthermore, among those with type 1 diabetes complicated by both nephropathy and hypertension, half are likely to progress to ESRD within ten years.[3]

Diabetic nephropathy progresses through distinct pathological phases. Initial functional changes at the glomerular level include hyperfiltration and increased perfusion, occurring prior to any overt clinical symptoms. As the disease progresses, structural changes occur, including thickening of the glomerular basement membrane, enlargement of the glomeruli, and expansion of the mesangial matrix. The rate of renal function decline after nephropathy onset varies significantly among individuals and is largely influenced by factors such as blood pressure control and glycemic regulation.[4]

The development and progression of diabetic nephropathy are driven by a combination of metabolic disturbances due to hyperglycemia, hemodynamic alterations, and genetic predispositions. Hemodynamic mechanisms involve the activation of vasoactive systems, including the renin–angiotensin–aldosterone system (RAAS) and the endothelin pathway. These lead to elevated levels of profibrotic mediators like transforming growth factor-β1 (TGF-β1), which further exacerbate systemic and intraglomerular pressure. [5]

Additionally, metabolic pathways contribute to kidney damage through mechanisms such as nonenzymatic glycation, increased activity of protein kinase C (PKC), and disruptions in polyol metabolism. Research also highlights the role of inflammatory mediators—such as cytokines, growth factors, and matrix metalloproteinases—in the pathogenesis of DN. Oxidative stress, resulting from an imbalance between reactive oxygen species and antioxidant defenses, appears to be a central factor in kidney injury related to diabetes. [6] [7]

Pathogenesis

Diabetic nephropathy (DN) is marked by structural changes such as glomerular hypertrophy, thickening of the basement membrane, and alterations in both glomerular and tubular membranes. These changes are accompanied by extracellular matrix accumulation, ultimately leading to glomerulosclerosis and tubulointerstitial fibrosis. Hyperglycemia affects multiple renal structures, triggering organ damage through various cellular mechanisms. These include alterations in gene expression, formation of advanced glycation end products (AGEs), activation of the polyol pathway,

abnormal stimulation of protein kinase C (PKC), and increased oxidative stress. Additionally, hyperglycemia induces several molecular responses involving growth factors and transcription factors. In response to chronic high glucose levels, transcription factors upregulate the expression of genes encoding pro-inflammatory and fibrotic cytokines and proteins Key molecules involved include transforming growth factor-beta (TGF-β), CCL2 (C-C motif chemokine ligand 2), fibronectin, osteopontin, decorin, thrombospondin, aldose reductase, and plasminogen activator inhibitor-1 (PAI-1).These molecules play critical roles in promoting inflammation, extracellular matrix production, and its impaired degradation, and are found in increased levels in individuals with type 2 diabetes. [8]

However, metabolic pathways activated by hyperglycemia alone may not be sufficient to cause kidney damage. Genetic predisposition, racial background, and environmental influences can interact with hemodynamic disturbances to exacerbate renal injury. These interactions promote AGE accumulation, sorbitol buildup, increased oxidative stress, and the activation of signaling pathways such as PKC and mitogen-activated protein kinase (MAPK). Albuminuria may develop in the initial stages of diabetic kidney damage and serves as a sensitive indicator for the progression of nephropathy.

The glomerular filtration barrier (GFB) is a highly specialized structure consisting of four key components: mesangial cells, the glomerular basement membrane (GBM), fenestrated endothelial cells, and podocytes. In diabetic nephropathy, this barrier undergoes significant pathological changes. These include thickening of the GBM, mesangial matrix expansion (sclerosis), endothelial cell dysfunction with damage to the glycocalyx layer, effacement and detachment of podocyte foot processes, and a reduction in podocyte number. Similar pathological processes also affect the tubular compartment of the nephron, where sustained extracellular matrix accumulation contributes to progressive tubulointerstitial fibrosis and further decline in renal function. [9]

1. Hyperglycemia-Induced Metabolic Changes

- **Advanced Glycation End Products (AGEs):** Chronic hyperglycemia leads to non-enzymatic glycation of proteins, forming AGEs that accumulate in the kidneys and promote inflammation and fibrosis.
- **Polyol Pathway Activation:** Excess glucose is shunted into the polyol pathway, leading to oxidative stress and cellular damage.
- **Hexosamine Pathway Activation:** Alters protein function and gene expression involved in extracellular matrix production.
- **PKC Activation (Protein Kinase C):** Hyperglycemia activates PKC, which contributes to increased vascular permeability and basement membrane thickening. [10]

2. Hemodynamic Changes

- **Glomerular Hyperfiltration:** Increased intraglomerular pressure due to dilation of afferent arterioles and constriction of efferent arterioles.
- **Renin-Angiotensin-Aldosterone System (RAAS) Activation:** Leads to vasoconstriction, increased blood pressure, and further glomerular damage. [11] [12]

3. Structural Changes in the Kidney

- **Mesangial Expansion:** Due to accumulation of extracellular matrix proteins.

- **Thickening of the Glomerular Basement Membrane (GBM):** Impairs filtration.
- **Glomerulosclerosis:** Scarring of glomeruli, leading to loss of kidney function.
- **Tubulointerstitial Fibrosis:** Damage extends to the tubules and interstitial tissues, worsening renal decline. [13]

4. Inflammatory and Oxidative Stress

- Infiltration of immune cells (macrophages, T-cells).
- Release of cytokines and growth factors like **TGF-β (Transforming Growth Factor-beta)** and **VEGF (Vascular Endothelial Growth Factor)**.
- Promotes fibrosis and capillary rarefaction. [14] [15]

Classification of Diabetic Nephropathy:

Diabetic nephropathy is classified into stages based on the progression of kidney damage, usually tied to changes in albumin excretion and glomerular filtration rate (GFR). The most widely accepted classification system is based on the Mogensen stages:

Classification of Diabetic Nephropathy:

Stage 1: Hyperfiltration (Early Stage)

- **Time**: Occurs soon after onset of diabetes.
- **GFR:** Increased (>125 mL/min).
- **Clinical signs:** No albuminuria.
- **Reversible:** Yes, with good glycemic control.
- **Causes:** Renal hyperfunction and hypertrophy

Stage 2: Silent Stage

- **GFR**: Normal or slightly increased.
- **Albumin excretion**: Normal (<30 mg/day).
- **Structural changes**: Glomerular basement membrane thickening and mesangial expansion.
- **Clinical signs**: No symptoms.

Stage 3: Microalbuminuria (incipient nephropathy)

- **Albumin excretion**: 30–300 mg/day (or 30–300 mg/g creatinine).
- **GFR**: May be normal.
- **Clinical signs**: Early predictor of nephropathy.
- **Reversible with treatment**: Possible with ACE inhibitors/ARBs and glycemic control**.**

Stage 4: Macroalbuminuria (overt nephropathy)

- **Albumin excretion:** >300 mg/day (proteinuria).
- **GFR:** Starts declining.
- **Clinical signs:** Hypertension, edema, overt proteinuria**,** Significant loss of kidney function

Stage 5: End-Stage Renal Disease (ESRD)

- **GFR:** Severely reduced (<15 mL/min/1.73 m^2).
- **Clinical signs:** Uremia, Major loss of kidney function usually requires dialysis or kidney transplant. [16]

Symptoms of Diabetic Nephropathy:

Signs of diabetic nephropathy typically do not become noticeable until around 80% to 90% of kidney function is lost. When symptoms do appear, they may include:

- Swelling (edema) in the face, hands, and feet.
- Nausea and vomiting.
- Persistent fatigue or tiredness.
- Shortness of breath (dyspnea).
- Decreased appetite.
- Foamy or bubbly urine – while occasional bubbles in urine can be normal, persistent or excessive foaming may indicate kidney dysfunction or a urinary tract infection.
- Trouble concentrating or episodes of confusion.
- Dry, itchy skin.
- Muscle cramps.
- A reduced need for insulin – as kidney function declines, insulin clearance is impaired, which may lead to lower insulin requirements. [17]

Diagnosis of Diabetic Nephropathy:

The following tests help diagnose diabetes-related nephropathy:

Urinalysis

- A urinalysis is a common test used to examine the physical, chemical, and microscopic properties of urine. Healthcare providers often use a dipstick test, where you'll be asked to provide a urine sample in a special container. A chemically treated paper strip (dipstick) is then dipped into the sample. If albumin (a type of protein) is present, the dipstick will change color, indicating potential kidney issues.
- For more accurate results, your provider may order a urine protein test, which is processed in a laboratory. This test measures the protein-to-creatinine ratio in your urine. A high ratio may indicate diabetic nephropathy.

Blood Tests

- Your healthcare provider may perform an estimated glomerular filtration rate (eGFR) test to assess how well your kidneys filter waste. This involves drawing a small blood sample, typically using a 21-gauge needle from a vein in your arm. The eGFR is calculated based on your blood creatinine levels and other health information. A low eGFR suggests impaired kidney function.

Imaging Tests

- To visualize kidney structure and blood flow, your provider may recommend:
- **Ultrasound –** a non-invasive test that shows kidney size and shape.
- Magnetic Resonance Imaging (MRI) and Computed Tomography (CT) scans are used to obtain detailed images of the kidneys and their vascular structures.

Kidney Biopsy

- A kidney biopsy involves removing a small sample of kidney tissue for microscopic examination. The procedure is usually performed under local anesthesia, accompanied by a mild sedative to help you remain calm. The provider uses a fine needle to collect the tissue sample through the skin.

Risk Factors of Diabetic Nephropathy

If you have diabetes, certain factors can increase your risk of developing diabetic nephropathy:

- Poorly controlled blood sugar levels (hyperglycemia).
- Unmanaged high blood pressure (hypertension).
- Smoking.
- Elevated blood cholesterol levels.
- Obesity.
- A family history of diabetes or kidney disease. [18]

Management of Diabetic nephropathy

In patients with classic diabetic nephropathy (DN), standard treatment continues to emphasize strict control of blood glucose and blood pressure. The main objective is to slow the progression of the disease and reduce albuminuria levels. This therapeutic focus is based on the premise that lowering albuminuria levels in individuals with diabetes is associated with improved kidney function and reduced cardiovascular disease (CVD) risk.

Goals of Blood Glucose Control

- Prevent or delay onset of microalbuminuria and macroalbuminuria.
- Reduce glomerular hyperfiltration and structural kidney damage.
- Minimize risk of hypoglycemia (especially in advanced kidney disease).

Target Glycemic Levels

According to ADA (American Diabetes Association) and KDIGO (Kidney Disease: Improving Global Outcomes):

Parameter	Target Range
HbA1c	~7% (individualized: 6.5–8%)
Fasting glucose	80–130 mg/dL
Postprandial	<180 mg/dL

Antidiabetic Drugs

Management of Hyperglycemia in Diabetic Nephropathy:

Managing hyperglycemia in patients with chronic kidney disease (CKD), particularly when accompanied by reduced glomerular filtration rate (GFR), presents significant challenges. Effective treatment requires careful selection of antidiabetic agents, considering altered pharmacokinetics and potential drug interactions. Patients with diabetic nephropathy (DN) are often older, have a longer history of diabetes, and frequently suffer from multiple comorbidities, which increases the risk of adverse drug interactions. Although treatment options have expanded over recent decades, the choices

remain limited in those with compromised renal function. Therefore, in-depth knowledge of how kidney impairment affects drug metabolism and excretion is essential when selecting appropriate therapies. Insulin remains a preferred treatment in advanced stages of CKD. However, certain oral antidiabetic medications can still be used, provided they are adjusted based on the patient's GFR.

Second-generation sulfonylureas:

- Agents like glipizide and gliclazide are considered safer for use in renal impairment because they are primarily metabolized by the liver and excreted as inactive metabolites.
- Glipizide should be used cautiously when the GFR drops below 30 mL/min.
- Glimepiride should be avoided if the GFR is less than 30 mL/min and used with caution when the GFR is below 60 mL/min.
- Gliclazide is generally safe and typically does not require dose adjustment. [19]

Meglitinides:

- Repaglinide can be used without dose modification, though careful monitoring is advised for GFR <30 mL/min.
- Incretin-based therapies: DPP-4 inhibitors and GLP-1 receptor agonists can generally be used in CKD patients, although some require dose adjustments depending on the specific agent and the level of renal function. [20]

SGLT2 inhibitors:

- These are usually not recommended in patients with GFR below 45 mL/min, due to reduced efficacy and potential safety concerns.

Insulin sensitizers:

- Biguanides (e.g., metformin) and thiazolidinediones (e.g.,pioglitazone) carry a lower risk of hypoglycemia.
- Metformin is excreted unchanged by the kidneys and can accumulate in renal impairment, increasing the risk of lactic acidosis.
- It is contraindicated at GFR <30 mL/min and should not be initiated in patients with GFR between 30–44 mL/min.
- Pioglitazone, however, is fully metabolized in the liver and does not require dose adjustment in renal impairment.

Alpha-glucosidase inhibitors:

Acarbose is minimally absorbed and largely metabolized by intestinal bacteria, but due to insufficient evidence in severe renal insufficiency, it should be avoided in patients with significantly reduced eGFR. [21]

DPP-4 Inhibitors:

Dipeptidyl peptidase-4 (DPP-4) inhibitors function by blocking the DPP-4 enzyme, thereby increasing endogenous levels of glucagon-like peptide-1 (GLP-1). This enhances insulin secretion while simultaneously suppressing glucagon release, leading to improved blood glucose control. These agents are generally safe for use in patients with renal impairment, although most require dose adjustments—

except for linagliptin, which can be used without modification regardless of kidney function. DPP-4 inhibitors are weight neutral and are recognized for their favorable safety profile.

Recent evidence indicates that DPP-4 inhibitors may offer multiple beneficial effects, including protection for both the heart and kidneys. Beyond their glucose-lowering capabilities, they demonstrate renoprotective properties through antioxidant and anti-inflammatory actions, as well as antifibrotic effects via inhibition of TGF-β-mediated signaling pathways.

DPP-4 is widely expressed in various tissues and cell types, with particularly high levels found in the kidneys, especially within the brush border of proximal tubular cells, suggesting a direct role in renal physiology and pathology. [22] [23]

SGLT2 Inhibitors:

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are oral antidiabetic agents that lower blood glucose levels by blocking glucose reabsorption in the kidneys, thereby promoting urinary glucose excretion and reducing hyperglycemia. Beyond their glucose-lowering effect, these drugs have demonstrated significant renoprotective benefits.

According to the EMPA-REG OUTCOME trial (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients), empagliflozin was associated with a 39% reduction in the risk of worsening nephropathy or death from cardiovascular causes.

Reduction of blood pressure through decreased vascular resistance,

- Weight loss,
- Lowering of intraglomerular pressure to prevent glomerular hyperfiltration,
- Decreased levels of proximal tubular injury biomarkers.

Since hypertension and obesity are independent risk factors for diabetic nephropathy, the additional benefits of SGLT2 inhibitors in managing these conditions further contribute to kidney protection.

Similarly, findings from the CANVAS trial (Canagliflozin Cardiovascular Assessment Study) demonstrated that canagliflozin slowed nephropathy progression by reducing albuminuria, delaying GFR decline, and lowering the risk of renal replacement therapy or death due to renal causes. [24]

Blood Pressure Control:

Findings from the UKPDS (United Kingdom Prospective Diabetes Study) revealed that a 10mmHg reduction in systolic blood pressure significantly decreased the risk of diabetic microvascular complications, including nephropathy. To manage blood pressure effectively in patients with diabetic nephropathy, the use of renin–angiotensin–aldosterone system (RAAS) inhibitors—such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs)—is strongly recommended.

This recommendation is backed by robust clinical evidence, as RAAS inhibition remains the most effective intervention to slow the progression of diabetic nephropathy (DN) to end-stage renal disease (ESRD). Several landmark trials have demonstrated the renoprotective benefits of these agents, including:

- IDNT (Irbesartan Diabetic Nephropathy Trial),

- IRMA-2 (Irbesartan in the Development of Diabetic Nephropathy in Patients with Type 2 Diabetes Mellitus),
- ROADMAP (Randomized Olmesartan and Diabetes Microalbuminuria Prevention), and
- The Captopril study.

These studies collectively confirmed that RAAS blockade can delay the onset and progression of nephropathy in diabetic patients.

However, combining ACE inhibitors with ARBs is not recommended, as studies have shown limited additional benefit over monotherapy and a higher risk of adverse effects, particularly hyperkalemia.

Additionally, non-dihydropyridine calcium channel blockers (e.g., diltiazem) have shown promise in slowing DN progression, based on data from experimental models and smaller clinical trials. In contrast, dihydropyridine calcium channel blockers have demonstrated variable effects on albuminuria, and their use requires careful consideration. [25]

Mineralocorticoid Receptor Antagonists:

In addition to its primary role in regulating sodium balance via mineralocorticoid receptor (MR) activation, aldosterone also contributes to inflammation and fibrosis, which can accelerate kidney damage. Several clinical studies have demonstrated that adding aldosterone antagonists to standard therapy provides additional renoprotective benefits, beyond those achieved with ACE inhibitors or ARBs alone.

Mineralocorticoid receptor antagonists (MRAs), such as spironolactone and eplerenone, have shown modest improvements in slowing kidney disease progression. However, their use requires careful monitoring, as they significantly increase the risk of hyperkalemia, particularly in patients with diabetes and chronic kidney disease (CKD). [26]

Endothelin Receptor Antagonists:

Endothelin-1 (ET-1) is a potent vasoconstrictor and mitogenic peptide with significant vasoactive, inflammatory, and profibrotic effects, playing a key role in the pathogenesis of cardiovascular disease and chronic kidney disease (CKD). In the kidneys, ET-1 contributes to renal fibrosis through multiple pathways. It promotes extracellular matrix accumulation, stimulates endothelial cell proliferation, induces epithelial-mesenchymal transition, and enhances the production of various cytokines and growth factors.

Phase III clinical trials investigating endothelin receptor antagonists, such as avosentan, initially showed promising results, including a reduction in albuminuria. However, the trials were prematurely discontinued due to a significant increase in fluid retention and congestive heart failure events among participants. These adverse effects were likely linked to the natriuretic blockade resulting from endothelin-B (ET-B) receptor inhibition. [27]

Vitamin D Receptor Activators (VDRA):

Role of Vitamin D in Diabetic Nephropathy:

1,25-Dihydroxyvitamin D_3 ($1,25(OH)_2D_3$) is the hormonally active form of vitamin D and functions as a key endocrine regulator with a broad range of physiological effects. Notably, it functions

as an inhibitor of the renin–angiotensin system (RAS). Activation of vitamin D receptors (VDRs) has demonstrated anti-inflammatory, immunomodulatory, and nephroprotective properties, forming the basis for the potential use of vitamin D receptor activators (VDRAs) such as paricalcitol and calcitriol in the control of diabetic nephropathy (DN).

Studies have shown that a reduction in 25(OH)D levels is associated with an increased prevalence of albuminuria, and a deficiency in vitamin D is independently linked to the progression of DN. As DN advances, vitamin D insufficiency tends to become more pronounced. A subanalysis of the PRONEDI study found that reduced levels of 25(OH)D is independently linked to an increased risk of diabetic nephropathy progression.

A systematic review of clinical trials evaluating the impact of active vitamin D (paricalcitol and calcitriol) in patients with chronic kidney disease (CKD) found that these agents significantly reduced proteinuria, especially when used alongside RAS blockade.

One of the key mechanisms underlying the renoprotective effects of VDRAs involves the protection of podocytes—specialized cells critical to the glomerular filtration barrier. VDR activation prevents podocyte injury and apoptosis, and increasing evidence supports the presence of VDRs in podocytes. The vitamin D/VDR signaling pathway has been shown to play a pivotal role in renal protection against DN.

Furthermore, $1,25(OH)_2D_3$ has been shown to reduce elevated levels of fibroblast growth factor 23 (FGF23), a molecule implicated in DN progression and podocyte injury.

Collectively, these findings provide strong support for the therapeutic use of vitamin D supplementation—particularly active forms—in both the prevention and management of diabetic nephropathy. [28]

Therapies Targeting Inflammation:

Pentoxifylline (PTF) is a methylxanthine-derived phosphodiesterase inhibitor primarily used to treat peripheral vascular disease due to its beneficial effects on microcirculatory blood flow. A meta-analysis has demonstrated that PTF exerts a significant antiproteinuric effect in patients with diabetic nephropathy (DN), which is believed to be mediated by a reduction in proinflammatory cytokines.

Therapies Targeting Free Radicals:

The human body possesses an antioxidant defense system to counteract the harmful effects of oxidants. Antioxidants are generally categorized into enzymatic and nonenzymatic types. Key enzymatic antioxidants include superoxide dismutase (SOD), catalase, glutathione peroxidase (GSH-Px), haem oxygenase-1 (HO-1), and thioredoxin, while major nonenzymatic antioxidants consist of glutathione (GSH), vitamins C and E, and β-carotene. These low molecular weight compounds are distributed across plasma, extracellular and intracellular fluids, lipoproteins, and cell membranes.

The principle behind radical-based therapy is to suppress or regulate the generation of reactive oxygen species (ROS) while enhancing endogenous antioxidant activity and/or employing exogenous antioxidant therapy. Given that hyperglycemia is a key driver of oxidative stress, tight glycemic control remains fundamental in the management of diabetic nephropathy (DN).

In addition, RAAS blockers, particularly telmisartan, an angiotensin II receptor blocker (ARB), have demonstrated therapeutic benefits in DN. Besides reducing albuminuria, telmisartan exhibits antioxidant effects by upregulating SOD activity and downregulating NOX (NADPH oxidase), an enzyme responsible for superoxide production. [29]

Resveratrol:

Resveratrol is a naturally occurring polyphenolic compound recognized for its wide-ranging antioxidant and anti-inflammatory effects. It has demonstrated beneficial effects in cardiovascular diseases and is increasingly recognized for its protective role in kidney diseases. As a potent antioxidant, resveratrol effectively scavenges reactive oxygen species (ROS), including superoxide anions, hydroxyl radicals, and peroxynitrite.

Beyond its direct antioxidant action, resveratrol exerts protective effects against age-related disorders, including renal injury, through the activation of Sirtuin 1 (SIRT1), a key regulator of cellular stress responses and longevity pathways. Due to these multifaceted mechanisms, resveratrol is considered a promising complementary therapeutic agent for the prevention and mitigation of kidney injury. [30]

Nrf2 Activators:

Nrf2 (nuclear factor erythroid 2–related factor 2) is a key transcription factor involved in maintaining redox homeostasis and regulating cellular detoxification mechanisms. Activation of Nrf2 plays a crucial role in reducing renal inflammation, primarily by suppressing the macrophage inflammatory response and inhibiting the transcription of proinflammatory cytokines such as IL-1 and IL-6. By inducing the expression of various antioxidant enzymes and cytoprotective genes, Nrf2 activation has emerged as a promising therapeutic target for managing diabetic complications, including diabetic nephropathy (DN).

One notable Nrf2 activator is bardoxolone methyl, a synthetic triterpenoid compound that not only activates Nrf2 but also inhibits NF-κB, a major proinflammatory signaling pathway. The BEAM study, which assessed 52 weeks of bardoxolone methyl treatment in patients with chronic kidney disease (CKD) and type 2 diabetes, demonstrated a significant improvement in estimated glomerular filtration rate (eGFR) at 24 weeks, which was sustained at 52 weeks. These findings underscored the potential of bardoxolone methyl as a therapeutic agent for chronic kidney disease (CKD).

However, the BEACON trial, which also reported increases in GFR, was prematurely terminated due to safety concerns, particularly fluid retention and heart failure. Despite this setback, the therapeutic relevance of Nrf2 activation in DN remains viable. Other Nrf2 activators, such as dimethyl fumarate, are currently approved for the treatment of multiple sclerosis, and ongoing research is evaluating the safety and efficacy of alternative bardoxolone formulations, such as RTA 402.

Therefore, although the use of bardoxolone methyl in diabetic nephropathy has certain limitations, the broader strategy of Nrf2 activation remains promising for future therapeutic approaches. Observations of improved renal outcomes in other diseases and successful use of Nrf2 activators in different clinical settings may renew interest in this pathway for treating diabetic nephropathy. [31]

Conclusion:

Diabetic nephropathy remains one of the most serious microvascular complications of diabetes mellitus, contributing significantly to end-stage renal disease worldwide. Understanding its complex pathophysiology—including hyperglycemia-induced oxidative stress, inflammation, and hemodynamic alterations—is essential for early diagnosis and effective intervention. Advances in biomarkers and imaging techniques now allow for earlier detection and more accurate monitoring of disease progression. Therapeutically, strict glycemic control, blood pressure management (particularly with RAAS inhibitors), and emerging agents such as SGLT2 inhibitors and GLP-1 receptor agonists are showing promise in slowing disease progression. A multidisciplinary approach, combining lifestyle modifications with pharmacologic therapies, remains the cornerstone of care. Continued research into novel molecular targets and personalized medicine will be crucial in improving outcomes and reducing the burden of diabetic nephropathy.

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The authors declare that they have no competing interest.

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