Article published online: 2024-11-21

Diabetic Nephropathy: Pathogenesis, Mechanisms, and Therapeutic Strategies

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Keywords
diabetic nephropathy, antihypertensive agents, ACE inhibitors and angiotensin II receptor, oxidative stress, advanced glycation end products

received 27.06.2024
accepted after revision 30.09.2024
published online 21.11.2024

Bibliography
Horm Metab Res 2025; 57: 7–17
DOI 10.1055/a-2435-8264
ISSN 0018-5043

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

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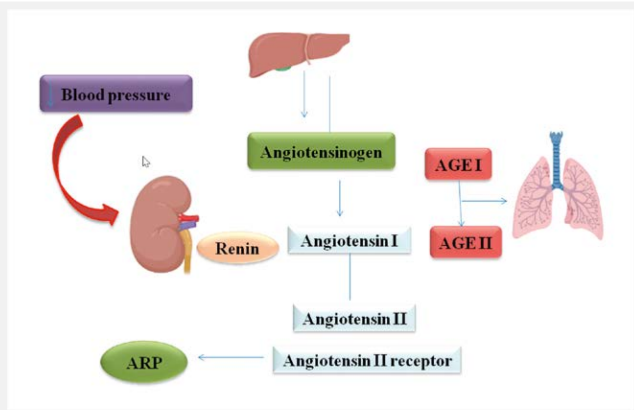
ABSTRACT

Diabetic nephropathy represents a predominant etiology of end-stage renal disease (ESRD) on a global scale, significantly impacting the morbidity and mortality rates of individuals with diabetes. The primary objective of this analysis is to furnish a comprehensive examination of the etiology, fundamental mechanisms, and treatment modalities for DN. The development of DN stems from a multitude of factors, encompassing a intricate interplay involving metabolic irregularities induced by hyperglycemia, alterations in hemodynamics, inflammatory responses, oxidative stress, and genetic susceptibility. Principal mechanisms encompass the generation of advanced glycation end products (AGEs), activation of protein kinase C (PKC), and overexpression of the renin-angiotensin-aldosterone system (RAAS). These processes precipitate glomerular hyperfiltration, hypertrophy, and eventually, fibrosis and scarring of the renal parenchyma. Initially, hyperglycemia triggers mesangial proliferation and thickening of the glomerular basement membrane in the incipient stages of DN, subsequently leading to progressive glomerular sclerosis and tubulointerstitial fibrosis. Inflammatory cascades, notably involving cytokines like TGF-β and NF-κB, play pivotal roles in the advancement of DN by fostering the accumulation of extracellular matrix and renal fibrosis. Inflammation pathways, particularly those involving cytokines like TGF-β and NF-κB, play essential roles in diabetic nephropathy progression by stimulating extracellular matrix accumulation and renal fibrosis. The presence of oxidative stress, worsened by dysfunctional mitochondria, contributes further to renal injury via lipid peroxidation and DNA damage. Current therapeutic approaches for diabetic nephropathy concentrate on optimizing glycemic control, controlling hypertension, and suppressing the renin-angiotensin-aldosterone system. Among antihypertensive medications, ACE inhibitors and angiotensin II receptor blockers are crucial for decelerating disease advancement.

Introduction

Diabetes is a prevalent worldwide challenge affecting 425 million individuals, with the International Diabetes Federation (IDF) projecting a rise to 630 million by 2045. Diabetic nephropathy (DN) (▶ **Fig. 1**), a critical complication, impacts one-third of diabetic patients and significantly contributes to cardiovascular morbidity and mortality, leading to substantial socioeconomic burdens [1]. Novel, efficient, and safe strategies against DN are urgently needed, grounded in a profound understanding of the intricate molecular mechanisms underlying the disease. The existing comprehension of DN's pathogenesis highlights numerous physiological imbalances, including hemodynamic irregularities, metabolic anomalies, oxidative stress, fibrosis, and renin-angiotensin system activation [2]. Despite various therapeutic measures to decelerate DN progression, their efficacy has been insufficient, necessitating the exploration of fresh strategies. Elevated levels of inflammatory mediators and immune cell infiltration into renal tissue are observed in DN patients, with upregulation of adhesion molecules and chemokines indicating inflammation's pivotal role in renal damage. Understanding the inflammatory mechanisms underpinning DN's evolution and progression will facilitate the discovery of novel therapeutic targets and the formulation of



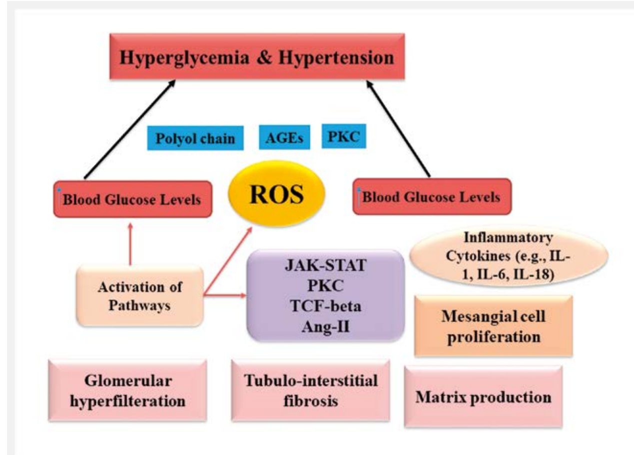
▶ **Fig. 1** Diabetic nephropathy: Each marker is connected to diabetes by a line, indicating their elevated levels in diabetic neuropathy conditions.

innovative anti-inflammatory strategies. Chronic low-grade inflammation and activation of the innate immune system are critical determinants in diabetes mellitus pathogenesis [3]. Elevated inflammatory markers in diabetic individuals serve as robust predictors for disease development. Metformin, the first-line medication for type 2 diabetes, reduces all-cause mortality and postpones renal failure onset in diabetic kidney disease [4]. Metformin has shown renoprotective effects in preclinical studies and has been linked to the Hippo pathway, with YAP overexpression associated with diabetic kidney damage. Effective pharmaceutical treatments targeting the Hippo pathway, such as metformin, may slow DKD progression [5]. SGLT-2 inhibitors, by reestablishing tubuloglomerular feedback, control hyperfiltration and offer renoprotective effects. Combination therapy may be relevant due to multiple kidney-level issues in DKD pathogenesis. Recent research shows that quercetin, a polyphenolic flavonoid, significantly reverses DKD by reducing oxidative stress and reactivating the Hippo signaling system, thereby preventing mesangial cell growth and improving renal function in diabetic rats [6]. With over 750 million CKD cases globally, categorizing chronic kidney disease (CKD) into diabetic kidney disease (DKD) and non-diabetic CKD reflects the rising prevalence of type 2 diabetes among CKD patients. In the US, 47 % of patients starting kidney replacement therapy in 2018 had end-stage kidney disease (ESKD), with a similar rate in South Korea in 2019 [7]. Novel anti-diabetic drugs in the past decade have proven to reduce blood glucose levels, with benefits and risks for heart and kidney health [8]. Thiazolidinediones may increase heart failure risk and fluid retention in T2D patients, whereas glucagon-like peptide-1 receptor (GLP-1R) agonists improve cardiovascular and renal outcomes. Dipeptidyl peptidase inhibitors also show benefits. SGLT-2 inhibitors significantly enhance cardiovascular and renal outcomes, offering benefits beyond glucose-lowering properties by stabilizing hemodynamics and regulating inflammation. GLP-1R agonists and SGLT-2 inhibitors lower blood pressure and potentially preserve kidney function. Despite advancements in DKD treatment, no notable medications have emerged for non-diabetic kidney disease [9]. Current clinical trials indicate SGLT-2 inhibitors can treat CKD and heart failure in non-diabetic patients, but more evidence is needed for their efficacy in specific non-diabetic renal disorders. Increased morbidity and mortality, particularly from cardiovascular causes, are linked to CKD, especially in patients with both CKD and diabetes mellitus (DM). Renal biopsies, though not routine in diabetic patients, are warranted when unusual presentations suggest other renal disorders that might benefit from precise therapeutic measures. Non-diabetic kidney disease incidence in diabetic patients is likely below 10 %, but this possibility should be considered, particularly with early significant renal issues in type 1 diabetes, suggesting non-diabetic renal disease [10]. Conditions like systemic lupus erythematosus can cause glomerulonephritis, requiring different treatments from DN. The absence of diabetic retinopathy in patients with significant renal complications might indicate another condition. The presence of red cell casts suggests conditions like glomerulonephritis or vasculitis, requiring specific treatments. Excessive proteinuria beyond what is expected from diabetic retinopathy or complications may indicate additional renal pathology. A family history of hereditary nephropathies or non-diabetic kidney diseases necessitates a biopsy to detect potential genetic conditions [11]. For individuals with classic DN, the primary therapeutic focus is on controlling glucose levels and blood pressure to halt DN progression and reduce albuminuria. While this strategy can decelerate disease progression, it often does not entirely halt or reverse it. Data indicate a continued rise in DN prevalence, underscoring the need for effective management strategies [12]. Intensive glycemic control plays a fundamental role in DN prevention and management. Studies like the United Kingdom Prospective Diabetes Study (UKPDS) and the Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation (ADVANCE) have shown that reducing HbA1c levels diminishes the risk of microvascular complications, including DN [13]. The recommended HbA1c target is around 7.0 %, with treatment customization to avoid severe hypoglycemia, particularly in advanced CKD patients. Second-generation sulfonylureas like glipizide and gliclazide, metabolized by the liver, are safer for renal impairment, while glimepiride should be used cautiously or avoided in severe renal dysfunction. Repaglinide can be used without dose adjustment, though caution is advised if GFR is below 30 ml/minute. DPP-4 inhibitors, which increase endogenous GLP-1 levels, are safe in renal impairment with dose adjustments, except for linagliptin, which does not require adjustment. SGLT-2 inhibitors are not generally recommended for significantly reduced eGFR, though they have shown benefits in reducing hyperglycemia and slowing kidney disease progression [14]. Metformin is contraindicated in severe renal impairment due to lactic acidosis risk. Pioglitazone, metabolized by the liver, does not require dose adjustment. Acarbose should be avoided in severe renal insufficiency due to limited safety evidence. Blood pressure control is crucial for slowing DN progression, with studies recommending a target of ≤ 130/80 mmHg for those with albuminuria [15]. ACE inhibitors and ARBs are first-line treatments for slowing DN progression, supported by studies like IDNT, RENAAL, and IRMA-2. Nondihydropyridine calcium channel blockers like diltiazem benefit DN progression, while dihydropyridines have varied effects on albumin excretion [16]. Reducing proteinuria is a key therapeutic goal in DN management. ACE inhibitors and ARBs are primary agents to reduce proteinuria, with newer agents like SGLT2 inhibitors showing promise in reducing proteinuria and providing renoprotective effects [17]. Obesity increases hyperfiltration and hormonal dysregulation, contributing to DN, and weight loss has been shown to reduce albuminuria. Protein restriction may help reduce proteinuria and slow disease progression. Statins are recommended to manage dyslipidemia, common in diabetic patients and contributing to cardiovascular risk. Smoking cessation reduces cardiovascular risk and may benefit kidney health [18]. Additional renoprotective benefits, when added to standard therapy, must be used cautiously due to hyperkalemia risk [19].

The Renin-Angiotensin-Aldosterone System (RAAS) blockade and Sodium-Glucose Cotransporter 2 (SGLT2) inhibitors represent two transformative pillars in the management of kidney and cardiovascular diseases, ushering in a new era of therapeutic possibilities and reshaping clinical paradigms [20]. These pharmacological interventions operate through intricate pathways deeply embedded in the pathophysiology of renal and cardiac disorders, offering benefits that transcend mere symptomatic relief [21]. By delving into their mechanisms of action, dissecting landmark trials, and examining practical considerations, we can grasp their pivotal roles in patient care and the ever-evolving landscape of personalized medicine [22].

Central to the pharmacological armamentarium against kidney and cardiovascular diseases is the Renin-Angiotensin-Aldosterone System (RAAS) blockade. This system, crucial for regulating blood pressure, electrolyte balance, and fluid homeostasis, orchestrates a cascade of hormonal events that, when dysregulated, contribute to the progression of renal and cardiac pathologies [23–27]. At the heart of RAAS function lies the conversion of angiotensinogen to angiotensin II, facilitated by angiotensin-converting enzyme (ACE), leading to vasoconstriction, sodium retention, and aldosterone secretion, thereby fostering hypertension, inflammation, fibrosis, and oxidative stress [28]. Mechanistically, ACE inhibitors and Angiotensin Receptor Blockers (ARBs) intervene at key points in this cascade, mitigating the deleterious effects of angiotensin II. While ACE inhibitors impede the conversion of angiotensin I to angiotensin II, ARBs selectively antagonize the angiotensin II type 1 receptor, thereby exerting renoprotective and cardioprotective effects [29]. Landmark trials such as RENAAL and IDNT have underscored the efficacy of these agents in slowing the progression of diabetic nephropathy, cementing their status as cornerstones in the management of renal diseases [30]. However, the ONTARGET trial has also shed light on the complexities of combination therapy, urging caution due to potential adverse events. Practically, vigilant monitoring of serum creatinine and potassium levels is paramount when initiating RAAS blockade, ensuring early detection of medication-induced alterations [31].

In parallel, the emergence of Sodium-Glucose Cotransporter 2 (SGLT2) inhibitors has revolutionized the therapeutic landscape, offering novel avenues for managing both diabetes and its associated renal and cardiovascular complications [32]. Initially designed to target hyperglycemia by inhibiting renal glucose reabsorption, SGLT2 inhibitors have transcended their primary indications, exhibiting multifaceted benefits beyond glycemic control. Mechanistically, these agents induce natriuresis by impeding glucose and sodium reabsorption in the proximal tubule, thereby reducing glomerular hyperfiltration and intraglomerular pressure, and ultimately slowing the progression of kidney disease [33]. Additionally, their



▶ **Fig. 2** Various mechanisms are involved in the pathogenesis of diabetic nephropathy. Reactive oxygen species (ROS), advanced glycation end products (AGEs), and protein kinase C (PKC) are among the key players. The abbreviation for angiotensin is Ang, which is known to modulate into transforming growth factor beta (TGF-β).

anti-inflammatory, antioxidant, and ketogenesis-promoting properties contribute to their renoprotective and cardioprotective effects [34]. Landmark trials like CANVAS and CREDENCE have unequivocally demonstrated the cardiovascular and renal benefits of SGLT2 inhibitors, solidifying their position as indispensable therapeutic agents in the armamentarium against diabetic kidney disease. However, the practical implementation of SGLT2 inhibitors necessitates awareness of potential adverse effects such as genital infections and volume depletion, alongside meticulous management during acute illness episodes [35].

Complementing these pharmacological advances are Glucagon-like peptide-1 (GLP-1) agonists, which have emerged as promising candidates for cardiovascular and renal protection in patients with diabetes [36, 37]. Derived from incretin hormones, GLP-1 agonists modulate insulin secretion, suppress glucagon release, delay gastric emptying, and induce satiety. Importantly, they exhibit anti-inflammatory effects, inhibit renal hemodynamic changes, and confer renal benefits beyond glycemic control. Landmark trials including LEADER, SUSTAIN-6 [38], and AWARD-7 have elucidated the cardiovascular and renal benefits of various GLP-1 agonists, further expanding the therapeutic armamentarium against diabetic kidney disease. Nevertheless, their practical implementation mandates careful dose titration and patient education regarding potential gastrointestinal side effects, alongside meticulous adjustment of concomitant antidiabetic medications to mitigate hypoglycemic risks [39].

Pathogenesis of Diabetic Nephropathy

Diabetic nephropathy (DN) is a multifaceted condition involving various interconnected mechanisms, primarily influenced by hyperglycemia [40]. The presence of hyperglycemia triggers multiple metabolic pathways that contribute to renal impairment, commencing with the polyol pathway, which enhances the generation of reactive oxygen species (ROS) as depicted in ▶ **Fig. 2** [41].

The oxidative stress induced by ROS results in both local and systemic inflammation, causing harm to crucial kidney cells like podocytes, mesangial cells, and endothelial cells, indispensable for the preservation of the glomerular filtration barrier, ultimately leading to proteinuria and tubule-interstitial fibrosis. Furthermore, hyperglycemia encourages the development of advanced glycation end-products (AGEs), which modify the structure and function of the kidney, culminating in thickening of the glomerular basement membrane and accumulation of matrix. This process is compounded by the activation of the protein kinase C (PKC) pathway, giving rise to the synthesis of endothelin-1 and vascular endothelial growth factor (VEGF), consequently inflicting additional harm on the glomerular capillaries. Additionally, the activation of PKC by ROS elevates levels of transforming growth factor-β (TGF-β) and angiotensin-II (Ang-II), fostering fibrosis and restructuring of the extracellular matrix [42, 43]. Ang-II assumes a critical role in the advancement of DN by stimulating the renin-angiotensin-aldosterone system (RAAS) [44]. Activation of systemic and intrarenal RAAS leads to elevated glomerular pressure, proteinuria, inflammation, and fibrosis. The effects of Ang-II are mediated through AT1 and AT2 receptors, with AT1 receptor stimulation causing vasoconstriction, sodium retention, and fibrosis. Components of intrarenal RAAS, such as renin and Ang-II, are upregulated in initial DN stages, contributing to continuous renal injury through oxidative stress and inflammation [45–48]. Moreover, the sodium-glucose cotransporter 2 (SGLT2) plays a role in the pathogenesis of DN by enhancing sodium reabsorption in the proximal tubules, exacerbating oxidative stress and mitochondrial dysfunction. The overexpression of SGLT2 induced by hyperglycemia, influenced by Ang-II, underscores the interconnectedness of glucose metabolism and RAAS in the progression of DN. Aldosterone, another component of RAAS, contributes to DN by activating TGF-β1 pathways, augmenting the production of extracellular matrix, and fostering fibrosis through ERK1/2-dependent mechanisms. The interaction of aldosterone with mesangial cells and its involvement in collagen deposition emphasize its significance in kidney fibrosis. Inflammatory cytokines, including IL-1, IL-18, and IL-6, also play a vital role in DN and are associated with albuminuria and decline in renal function. The nuclear factor-κB (NF-κB) pathway acts as a pivotal regulator of inflammation in DN, encouraging the generation of proinflammatory cytokines and adhesion molecules, thereby contributing to kidney damage. The Janus kinase/signal transducers and activators of transcription (JAK-STAT) pathway represents another crucial mechanism activated in DN [49]. It facilitates the impact of hyperglycemia, mechanical stress, AGEs, and Ang-II, resulting in NF-κB activation and a cyclic pattern of inflammation and renal injury. Glomerular hypertension due to glucose-induced dilation of glomerular afferent arteries also contributes to albuminuria and reduction in eGFR, highlighting the hemodynamic alterations in DN. Kidney hypoxia, arising from increased energy consumption and diminished oxygen delivery due to glomerular hyperfiltration and interstitial fibrosis, stands as a significant factor in the progression of DN. Dysregulated autophagy, particularly involving the mammalian target of rapamycin complex 1 (mTORC1), further exacerbates renal damage. Inhibition of mTORC1 shows potential in slowing down the progression of DN, underscoring the importance of regulating autophagy in DN [50–56].

Role of Free Radicals in Diabetic Nephropathy

Reactive oxygen species (ROS) and reactive nitrogen species (RNS), which are other names for free radicals (FRs), are constantly being produced during cell metabolism [57]. Both the normal metabolic products of endothelial cells and those produced under altered environmental conditions – such as in water and organic molecules under the influence of UV or ionizing radiation, toxic substances, or pathological conditions – can be classified as these. Super-oxides are released by phagocytes and nitric oxide (NO) activation. Unpaired electrons in their outer orbitals indicate that FRs are extremely reactive particles with one or more missing electrons. Primarily, mitochondria are the source of free radicals (FRs), especially via the action of mitochondrial NADPH oxidase (NOX). This process begins with the superoxide radical ($O_2^{\bullet}$), which then transforms into more reactive forms such as hydrogen peroxide, hydroxyl radicals ($^{\bullet}OH$), peroxyl and hydroperoxyl radicals ($ROO^{\bullet}$), singlet oxygen ($^1O_2$), nitric oxide radicals ($NO^{\bullet}$), and nitrogen dioxide radicals ($NO_2^{\bullet}$). ROS are essential for the immune system when present in low to moderate concentrations because they eliminate foreign substances, change and regenerate cellular membranes, control apoptosis, and regulate the creation of prostaglandins, leukotrienes, and thromboxanes. In addition, ROS govern the intracellular signal transmission pathways that govern various other activities such as cell development and differentiation [58].

Oxidative stress (OS) is caused when the antioxidant defence system's (AOD) equilibrium between the generation of reactive oxygen species (ROS) and their detoxification is upset under pathological circumstances [59]. According to Sies, oxidative stress syndrome (OS) is an imbalance that results in molecular damage or altered redox signaling and regulation between pro- and antioxidants. Overproduction of ROS leads to the oxidation of macromolecules, including proteins, DNA, and lipids, which results in long-lasting alterations. OS influences redox-sensitive transcription factors, endothelial signal transduction, and vascular permeability in addition to encouraging leukocyte adhesion. An important pathogenetic component of many diseases, such as diabetes, cancer, heart disease, rheumatoid arthritis, neurological conditions, and illnesses of the liver, kidney, and lung, is OS. OS is a major element in ageing and age-related disorders since the chance of having these conditions rises with age [60].

Current theories about OS emphasize its function in cell division, apoptosis, and signaling. Current knowledge takes into account both direct ROS damage to DNA, lipids, and proteins as well as indirect impacts through signaling pathways that are redox- or ROS-dependent [61]. It also highlights pathologically rectifying OS and evaluating pro-antioxidant status, and it connects OS with carbonyl stress, differentiating between systemic and local OS. When evaluating redox potential and the course of a disease, OS indicators are essential. Since ROS have brief half-lives and are unstable, it is challenging to measure them directly. Rather, longer-lasting oxidation products derived from biomolecules are employed [62]. Products of lipid peroxidation (LPO) include 4-hydroxynonenal (HNE), F2-isoprostanes, thiobarbituric acid-reactive compounds (TBARs), and malondialdehyde (MDA). Advanced oxidation protein products (AOPPs), advanced glycation end-products (AGEs), methylglyoxal (MGO), and protein carbonyls are the products of protein oxidation, whereas 8-hydroxyguanosine (8-OHG) and

8-hydroxy-2′-deoxyguanosine (8-OHdG) are the products of nucleic acid oxidation. The antioxidant superoxide dismutases (SODs), catalases (CATs), glutathione peroxidases (GPx), peroxiredoxins (Prdx), glutathione S-transferases (GSTs), and other antioxidant enzymes, along with non-enzymatic antioxidants like reduced glutathione (GSH), vitamins, ceruloplasmin, ferritin, and carnosine, neutralize ROS. Several biomarkers should be measured in order to minimise erroneous results because OS is a ubiquitous and non-specific condition [63].

Renal oxidative phosphorylation and fatty acid β-oxidation are two mechanisms that produce a considerable amount of reactive oxygen species (ROS) and are crucial for the kidneys, which are second only to the heart in terms of mitochondrial abundance in (DN). DN progression is mostly caused by OS and mitochondrial dysfunction. Endocrine system (OS) modulates apoptosis and cell cycle arrest in a variety of renal cells, including podocytes and endothelial cells [64]. Kidney damage is a result of pathways such as PI3K/Akt, TGF-β1/p38-MAPK, and NF-κB that cause endothelial apoptosis, inflammation, autophagy, and fibrosis. With the discovery of iron overload, decreased antioxidant capacity, increased ROS, and LPO in diabetic kidney models, the iron-dependent LPO mechanism ferroptosis has been a prominent topic of research in the progression of DN [65].

Hyperglycemia sets off a series of metabolic reactions that deteriorate vascular walls, mostly by forming reactive oxygen species within the mitochondria. Beyond the mitochondria, these reactive components cause damage to DNA and mitochondrial enzymes. They also set off other harmful processes, such as endothelial dysfunction, AGE formation, PKC and NF-κB activation, and epigenetic modifications. While FRs are transient, the harm they inflict on proteins, lipids, and nucleic acids endures, playing a role in "metabolic memory," a process whereby initial hyperglycemic consequences result in enduring cellular abnormalities [66]. Managing the complications of diabetes requires effective early glycemic control. Significant effects on arterial walls are caused by AGEs, which also enhance gene expression, thrombosis, sclerosis, platelet aggregation, synthesis of cytokines and growth factors, proliferation, and mutation frequency [67]. Renal cells are impacted by AGEs binding to RAGEs, which causes cell cycle arrest and inflammation, as well as increased production of ROS and OS [68–70].

Multiple STZ injections are one type of experimental DN model that mimics DN by causing OS and mitochondrial malfunction, loss of pancreatic beta cells, and decreased insulin output. When albuminuria and histological kidney abnormalities occur first in STZ-induced diabetic rats, changes in mitochondrial bioenergetics occur first. In early-stage diabetes without distinct glomerular disease, mitochondrial fragmentation and a decrease in ATP concentration are predictive markers. With the potential to sustain mitochondrial function, PGC-1α coactivators and NRF1 and TFAM transcription factors may be involved in the progression of DM, which is characterized by mitochondrial dissociation, OS production, and glomerular alterations. Microbiological ROS production, decreased membrane potential, increased apoptosis, and decreased PINK expression are observed in db/db mice models of obesity, diabetes, and dyslipidemia [71].

Lactic acidosis and hypoxia in diabetic kidney disease (DKD) mice lead to anomalies in the mitochondria and fibrosis. Rats with DM brought on by STZ show elevated MDA and glucose levels, OS indices, and overall oxidant status. Increased levels of MDA, NO, NF-κB p65, and TNF-α in the kidneys, along with decreased levels of GSH, SOD, and Bcl-2, are indicative of heightened inflammatory cytokines, OS, and nitrosative stress. Observations include elevated blood glucose levels, impaired kidney and insulin function, sclerosis, interstitial fibrosis, OS responses, and activation of the TGF-β1 pathway. Defective mitophagy, reduced mitochondrial membrane potential, ROS production, and aberrant mitochondrial function are indicators of the progression of DN. Increased ROS generation and decreased endothelial NO synthase are associated with the progression of DN, while GECs exhibit elevated mitochondrial superoxides and DNA damage [72].

Significant OS activation is shown in clinical investigations on DN, with elevated levels of urine 8-OHdG, MDA, AGEs, protein carbonyls, TBARs, and AOPP in the serum. ROS production in diabetic patients is facilitated by dysfunctional mitochondria and NOX1 in the liver. Increased OS, inflammation, apoptosis, fibrosis, and modified glomerular filtration barriers are all involved in the development of DN. Hyperlipidemia, OS, AGE buildup, and inadequate glycemic management are all linked to microalbuminuria. Moreover, excessive lipid buildup in podocytes associated with DN causes insulin resistance, ER stress, inflammatory responses, cytoskeleton remodeling, and mitochondrial OS lipotoxicity. Inflammation, fibrosis, and vascular permeability are caused by hyperglycemia, which also elevates cytokine and chemokine levels and activates signaling pathways [73].

When ROS are produced excessively, TGF-β1 rises and causes tubulointerstitial fibrosis in DN patients. In DN, elevated amounts of carbonyl groups, ceruloplasmin, CAT, thiol, and glucose are seen. For DN patients, determining LPO, VEGF products, podocyte damage indicators, and immuno-inflammatory factors is essential. Studies reveal a positive correlation between the length of the disease and elevated oxidative damage to DNA and lipids in T1DM males with early-stage DN. Renal hypertrophy and chronic inflammation are caused by circulating AGE levels, which are correlated with DN risk and alter TGF-β1 and RAAS functioning. When AGE-mediated RAGE activation occurs, NOX produces ROS and RNS, which ages the kidneys and causes OS in DN [74].

Conventional and Advance Therapy in Diabetic Nephropathy

Proteinuria is decreased and the development of both diabetic and nondiabetic nephropathies is slowed down by blood pressure control achieved through renin-angiotensin system (RAS) blockage [75]. When renal function deteriorates, it is crucial to carefully alter dosages or avoid specific medications in order to optimize glycemic control with antihyperglycemic medications, such as insulin. Because they lower blood pressure, albuminuria, and urine endothelin, statins like rosuvastatin, cerivastatin, and simvastatin are helpful in diabetic nephropathy [76]. The incidence of diabetic nephropathy cannot be reduced by standard multifactorial therapy, which is still difficult to administer and insufficient in managing blood pressure, glucose management, and cholesterol levels. The length of medication will determine whether statins have any notable renoprotective effects [77]. Studies like the ADVANCE, BENEDICT, and ROADMAP trials have shown promising results in primary prevention. These investigations demonstrated that the incidence of microalbuminuria was decreased, and its beginning was postponed by treatments with ACE inhibitors or angiotensin receptor blockers (ARBs). Presumably, patients treated with perindopril/indapamide saw reduced blood pressure and microalbuminuria; on the other hand, the ROADMAP study found that olmesartan postponed the beginning of microalbuminuria. Furthermore, the RASS trial discovered that losartan and enalapril slowed the advancement of diabetic retinopathy. ACE inhibitors or ARBs are crucial for individuals with microalbuminuria, independent of blood pressure levels, as treatment attempts to impede the progression to clinical albuminuria and encourage regression towards normoalbuminuria. New hypoglycemic medications including SGLT2 inhibitors (SGLT2is) and GLP-1 receptor agonists (GLP-1RAs), which not only control hyperglycemia but also lessen cardiovascular consequences and safeguard renal function, have recently made significant strides in the treatment of diabetic kidney disease [78]. Due to their various mechanisms of action, certain novel antidiabetic medications for type 2 diabetes have demonstrated benefits in type 1 diabetes, even if insulin is still the major treatment for the condition. Through improving renal tubular function and raising natriuresis and diuresis, GLP-1RAs improve kidney outcomes in patients with type 2 diabetes. By preventing sodium-hydrogen exchanger 3 (NHE3) and balancing afferent and efferent vasoconstriction, they have an impact on renal hemodynamics. Not only do GLP-1RAs boost GFR by inducing glomerular hyperfiltration, but they also have anti-inflammatory and antioxidant properties that may enhance renal function. GLP-1RAs have been demonstrated in studies such as ELIXA and LEADER to mitigate the onset of macroalbuminuria and unfavorable renal outcomes [79]. Notably, GLP-1RAs such as liraglutide, semaglutide, and dulaglutide have been proven to significantly improve eGFR and reduce albuminuria. Significant renal protection is also offered by SGLT2 inhibitors, which inhibit glucose reabsorption by acting on renal tubules [80].

Blood pressure is lowered, weight is lost, and volume is depleted. Empalagliflozin, canagliflozin, and dapagliflozin are examples of SGLT2 inhibitors that, even in patients with advanced or non-diabetic CKD, minimize the risk of CKD progression and improve renal pathology, according to clinical research. Prolonged preglomerular vasoconstriction and decreased postglomerular vascular resistance are the mechanisms by which these medications diminish glomerular hyperfiltration; large-scale experiments have proven this effect [81]. DPP-4 inhibitors increase levels of GLP-1 and GIP, aiding in glucose control, and are suitable for advanced T2DM and kidney dysfunction. They reduce renal fibrosis and proteinuria independently of glycemic control, though their impact on cardiovascular outcomes in diabetic nephropathy is neutral. Finerenone, a new mineralocorticoid receptor antagonist, has shown significant benefits for renal and cardiovascular systems in T2DM patients with CKD. The FIDELIO-DKD and FIGARO-DKD trials demonstrated that finerenone reduces the risk of kidney failure, cardiovascular events, and mortality. Combining finerenone with GLP-1RAs or SGLT2 inhibitors further enhances these benefits. Novel lipid-lowering drugs are crucial for managing dyslipidemia in CKD patients, who often have high LDL-C and low Apo A-I levels. While statins provide benefits in early-stage CKD, their effectiveness in advanced CKD or ESRD, especially for cardiovascular events, is limited. Combination therapies and PCSK9 inhibitors have emerged as effective options for reducing LDL-C and cardiovascular risk in CKD. PCSK9 inhibitors, such as evolocumab, have shown promise in decreasing cardiovascular events and improving outcomes in CKD patients [82].

An overview of the randomized controlled trials (RCTs) with renal illness as their primary endpoint that are referenced in the text is shown in ▶ **Table 1**.

Antioxidant Therapy

Effective antioxidant medicines must be used promptly and in the right dosage when treating illnesses where oxidative stress (OS) is the underlying pathophysiology as shown in ▶ **Table 2**. These substances aid in restoring oxidative metabolism by balancing the pro- and antioxidant systems. The metabolic effects of antioxidant supplements have been shown in vitro, especially with regard to insulin activity [83]. However, the precise mechanisms of action of these supplements have not yet been thoroughly established in clinical investigations. Various phytochemicals, such as dietary antioxidants, resveratrol, curcumin, α-lipoic acid (α-LA), α-tocopherol (vitamin E), vitamin C, and selenium, are used in modern antioxidant therapy for diabetic nephropathy (DN). These are employed for the treatment of many systemic disorders in addition to diabetes. An advantage in nephroprotection against OS may come from focusing on the particular causes of renal reactive oxygen species (ROS) in diabetic kidney disease (DN). Rich in fat-soluble antioxidant properties, vitamin E can influence gene and protein functions and guard against oxidative damage to the lipid components of cell membranes. α-Tocopherol is the most active form among its eight variants. The effects of α-tocopherol on tubulointerstitial damage, TGF-β1 expression inhibition, and kidney and plasma MDA concentration reduction have all been demonstrated in experimental and clinical trials [84]. While it had no effect on IL-6 or CRP levels, a 10-week dose of 600 IU of α-tocopherol increased endothelial function biomarkers in hemodialysis patients. Supplementing DN patients with albuminuria with tocotrienols and tocopherols has been demonstrated to be beneficial. A one-year study found that tocotrienol-enriched vitamin E accelerated the course of diabetic kidney disease (DN), especially in stage 3 cases. Together with raising GFR, it also lowered serum creatinine levels. Because of its anti-inflammatory and antioxidant qualities, vitamin E helps diabetics control their glucose levels and prevent issues before they arise. Calcium-phosphate and skeletal homeostasis are influenced by vitamin D, especially by its active form 1,25$(OH)_2$D3. It can prevent the advancement of diabetes mellitus and maintain the integrity of the glomerular filtration barrier, according to studies, albeit the best dosage and timing for supplementation are unknown. It has been demonstrated that vitamin D lowers proteinuria and enhances renal podocyte function. It is associated with improved lipid profiles and decreased microalbuminuria levels. However, supplementation may not have a significant positive impact on other indicators, such as serum creatinine or GFR. In DN models, paricalcitol, a vitamin D receptor activator, has improved structural alterations and decreased proteinuria [85]. In diabetic animals, vitamin D therapy has also been shown to lower hyperglycemia and raise insulin concentrations.

▶ **Table 1** An overview of the randomized controlled trials (RCTs) with renal illness as their primary endpoint that are referenced in the text.

Experimental drug	Study, Year	Class	Kidney outcome	Reference
Losartan	RENAAL, 2001	ARB	Increase of serum	[90]
Telmisartan	DETAIL, 2005	ARB	GFR changed	[91]
Captopril	CSG Captopril, 1993	ACEi	Creatinine concentration changed	[92]
Finerenone	FIDELIO-DKD, 2020	NS-MRA	> 40 % decrease in eGFR	[93]
Irbesartan	IDNT, 2001	ARB	ESKD	[94]
Avosentan	ASCEND, 2010	ETA RA	ESKD	[95]
Zibotentan + Dapaglifozin	ZENITH-CKD, 2023	ETA RA + SGLT2i	UACR changed	[96]
NCT05182840, 2024	BI 690517	ASI ± SGLT2i	UACR Changed	[97]

▶ **Table 2** Therapeutic approach for the management of diabetic nephropathy.

Intercession	Target [Ref]
Antihypertensive agents	BP ≤ 130/80 mmHg for albuminuria ≥ 30 mg/d [102]
Dietary protein restriction	0.8 g/kg/d in GFR < 30 mL/min/1.73 m^2 [103]
Lipid-lowering agents (statins)	LDL-C < 70–100 mg/dl [104]
Smoking cessation	Abstinence [105]
Dietary salt restriction	< 5 g/d [106]
Antiplatelet therapy	Thrombosis prophylaxis [107]

Other antioxidants can be restored by vitamin C, a water-soluble vitamin with potent antioxidant action. It has an abundance of green veggies and citrus fruits. Vitamin C treatment has considerably decreased glomerular and tubulointerstitial sclerosis, proteinuria, and albuminuria in diabetic rats. It also improves renal hemodynamics and oxidative stress markers when combined with other treatments like captopril or metformin [86]. Resveratrol, found in plants, foods, and beverages like red wine, has cardioprotective, renoprotective, and antidiabetic properties. It regulates various pathways responsible for ROS and AGE production, ER inflammation, and autophagy. Resveratrol stimulates antioxidant enzyme activity, reduces ROS formation, and protects against OS by activating pathways like AMPK/SIRT1/Nrf2. Studies in diabetic models show that resveratrol improves kidney function, reduces inflammatory markers, and mitigates renal damage. Combined with other treatments like ramipril, it has shown to reverse early DN stages. Resveratrol enhances mitochondrial function, reduces oxidative damage, and could be beneficial as an adjunct to traditional diabetes therapy [87]. Curcumin, derived from turmeric, has anticancer, anti-inflammatory, hypoglycemic, and antioxidant properties. It improves insulin resistance and glycemic control and reduces triglycerides and cholesterol in T2DM patients. In diabetic rat models, curcumin has shown to reduce kidney damage, oxidative stress markers, and inflammatory cytokines. It activates antioxidant pathways like NRF2/KEAP1/ARE and improves renal function. However, its poor solubility and absorption in the gastrointestinal tract limit its effectiveness [88], leading to the development of nanocurcumin for better bioavailability and efficiency. α-Lipoic acid (α-LA) is a natural antioxidant that reduces oxidative damage, inflammation, and renal fibrosis. It improves glucose levels, reduces AGE formation, and maintains kidney structural integrity in diabetic models. Clinical trials show that α-LA reduces urinary albumin excretion and improves antioxidant enzyme activity. Combining α-LA with other treatments like valsartan enhances its protective effects against DN. Coenzyme Q10 (CoQ10), a fat-soluble antioxidant, is essential for mitochondrial ATP production and reducing ROS. It shows promise in DN treatment by improving fasting plasma glucose, HbA1c, cholesterol levels, and oxidative stress markers. Combined with other treatments, CoQ10 improves renal function and mitigates DN-related damage. Mitochondrial-directed antioxidants (MTAs) and mimetics of antioxidant enzymes offer therapeutic benefits for DN by targeting specific sources of ROS. Compounds like MitoQ and enzyme simulators such as SOD and GPx have shown positive effects on renal function and reducing oxidative damage in experimental models [89].

Clinical Features and Progression of Diabetic Nephropathy

The progression of diabetic nephropathy from microalbuminuria to macroalbuminuria signifies a pivotal shift in renal function, indicative of worsening glomerular injury and compromised filtration capacity. Microalbuminuria, characterized by the presence of moderately increased urinary albumin excretion, serves as an early marker of renal dysfunction, often preceding overt nephropathy [98]. As the disease advances, the transition to macroalbuminuria, marked by substantial albuminuria, heralds a critical stage in diabetic kidney disease progression, reflecting extensive glomerular damage and impaired barrier function. Concurrently, glomerular filtration rate (GFR) undergoes a progressive decline, mirroring the relentless deterioration of renal function inherent to diabetic nephropathy [99]. This decline in GFR, indicative of reduced kidney function and impaired filtration capacity, underscores the severity of renal injury and portends an increased risk of adverse outcomes. End-stage renal disease (ESRD) represents the culmination of diabetic nephropathy's relentless progression, characterized by irreversible loss of renal function necessitating renal replacement therapy for survival. The development of ESRD imposes a profound burden on affected individuals, requiring chronic dialysis or kidney transplantation to sustain life. Moreover, ESRD substantially impacts patients' quality of life, contributing to physical and psychological distress and imposing significant financial costs on healthcare systems. The prevention and management of ESRD constitute a critical aspect of diabetic nephropathy care, emphasizing the importance of timely intervention and aggressive risk factor modification to delay disease progression and mitigate adverse outcomes. Beyond its profound impact on renal function, diabetic nephropathy exerts a substantial toll on cardiovascular health, significantly increasing the risk of cardiovascular morbidity and mortality. The bidirectional relationship between diabetic nephropathy and cardiovascular disease underscores the intricate interplay between renal and cardiovascular pathophysiology. Individuals with diabetic nephropathy face an elevated risk of developing cardiovascular complications, including coronary artery disease, myocardial infarction, heart failure, and stroke. Cardiovascular disease contributes to the progression of diabetic nephropathy, exacerbating renal injury through hemodynamic alterations, endothelial dysfunction, and systemic inflammation. The synergistic effects of renal and cardiovascular pathology underscore the importance of comprehensive management strategies addressing both conditions simultaneously [100].

Practical Considerations and Future Directions

Adverse effects and monitoring guidelines are integral aspects of managing diabetic nephropathy and its treatment modalities. As patients with diabetic nephropathy often present with multiple comorbidities and require complex medication regimens, vigilance regarding adverse effects is paramount to optimize therapeutic outcomes while minimizing harm. Common adverse effects associated with medications used in diabetic nephropathy management, such as renin-angiotensin-aldosterone system (RAAS) inhibitors and sodium-glucose cotransporter 2 (SGLT2) inhibitors, include electrolyte imbalances, renal dysfunction, hypotension, and hyperkalemia. Regular monitoring of serum electrolytes, renal function, blood pressure, and glycemic control is essential to detect adverse effects promptly and adjust treatment regimens accordingly. Furthermore, patient education plays a pivotal role in fostering medication adherence and empowering individuals to actively participate in their care [103]. Patient education initiatives should focus on medication adherence, lifestyle modifications, dietary restrictions, and self-monitoring techniques, emphasizing the importance of adhering to prescribed treatment regimens to optimize renal and cardiovascular outcomes. Adherence strategies tailored to individual patient needs, preferences, and socioeconomic circumstances can enhance treatment adherence and improve long-term adherence to therapy. Additionally, the potential for combination therapies in diabetic nephropathy management offers promising avenues for achieving synergistic therapeutic effects and addressing multiple pathophysiological pathways implicated in disease progression. Combination therapy involving RAAS inhibitors, SGLT2 inhibitors, and novel agents targeting inflammation, oxidative stress, and fibrosis holds promise for enhancing renoprotective efficacy and delaying disease progression. Moreover, emerging research in diabetic nephropathy continues to uncover novel pathophysiological mechanisms and therapeutic targets, driving innovation and shaping future treatment paradigms. Areas for future investigation include elucidating the role of gut microbiota, exploring epigenetic modifications, and leveraging precision medicine approaches to tailor treatment strategies to individual patient profiles. By embracing emerging research findings and fostering interdisciplinary collaborations, clinicians and researchers can advance our understanding of diabetic nephropathy and develop novel therapeutic interventions to improve patient outcomes and reduce the global burden of this debilitating complication of diabetes [101].

Conclusion

A summary of crucial discoveries and insights in diabetic nephropathy highlights the intricate nature of this intricate renal condition. Fundamental to comprehending diabetic nephropathy is the acknowledgment of its pathophysiological mechanisms, encompassing oxidative stress induced by hyperglycemia, inflammation, and activation of the renin-angiotensin-aldosterone system (RAAS), all contributing to glomerular damage, proteinuria, and gradual renal function deterioration. Furthermore, the interaction between diabetic nephropathy and cardiovascular disease underscores the significance of holistic management strategies addressing both renal and cardiovascular risk factors to enhance clinical outcomes and decrease mortality rates. Recent research has elucidated novel therapeutic targets, such as sodium-glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists, showing potential renoprotective benefits beyond glycemic control and promising to reshape the therapeutic landscape of diabetic nephropathy. Additionally, advancements in precision medicine and personalized treatment herald a new phase of tailored interventions aiming to optimize outcomes and decrease the global burden of diabetic nephropathy. The implications for clinical practice in managing diabetic nephropathy are extensive, stressing the significance of early identification, risk assessment, and proactive intervention to decelerate disease progression and alleviate unfavorable consequences. Healthcare providers play a crucial role in implementing evidence-based protocols for screening, monitoring, and managing diabetic nephropathy, incorporating multidisciplinary approaches to cater to the varied requirements of affected individuals. Patient education and empowerment are key elements of clinical practice, fostering cooperation between healthcare professionals and patients to enhance medication adherence, lifestyle adjustments, and self-care strategies. Moreover, proactive management of comorbidities like hypertension, dyslipidemia, and cardiovascular disease is vital to diminish the likelihood of advancing to end-stage renal disease and cardiovascular incidents. By adopting a comprehensive care approach and utilizing innovative treatments and technologies, healthcare providers can enhance the quality of life and prognosis for individuals with diabetic nephropathy, ultimately decreasing the socioeconomic impact linked with this severe diabetes complication. Prospects in managing diabetic nephropathy hold potential for enhancing our comprehension of disease development, refining diagnostic standards, and formulating targeted therapies tailored to individual patient profiles. Research endeavors directed towards elucidating new pathophysiological mechanisms, such as gut microbiota dysbiosis, epigenetic alterations, and immune system dysregulation, provide fresh insights into disease advancement and potential therapeutic targets. Additionally, the integration of biomarkers and imaging techniques into clinical practice has the potential for early detection of renal impairment and prognostic classification of patients at risk of unfavorable outcomes. Moreover, the emergence of artificial intelligence and machine learning algorithms presents opportunities for predictive modeling and precision medicine strategies, allowing for personalized risk evaluation and treatment enhancement. By promoting collaboration between fundamental researchers, clinicians, and industry collaborators, future research initiatives can expedite the translation of scientific breakthroughs into clinical practice, ushering in a new era of precision medicine and improved outcomes for individuals with diabetic nephropathy.

Contributors' Statement

SD has written the manuscript and communicated the manuscript, MS has designed the work and supervised the entire work.

Conflict of Interest

The authors declare that they have no conflict of interest.

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