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Review Article

DIABETIC NEPHROPATHY: A NARRATIVE REVIEW FROM PATHOPHYSIOLOGY TO ITS TREATMENT

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ABSTRACT

One of the most dangerous microvascular side effects of diabetes mellitus is diabetic nephropathy (DN), which is the primary cause of end-stage renal disease globally. Because type 2 diabetes, obesity, sedentary behavior, and metabolic syndrome are becoming more common, its occurrence is continuously rising, especially in developing countries. Persistent hyperglycemia, hemodynamic abnormalities, oxidative stress, hereditary vulnerability, and activation of inflammatory and profibrotic pathways are all part of the complex pathophysiology of diabetic kidney disease (DN), which leads to progressive renal impairment. Clinically, DN develops gradually and frequently shows no symptoms at first. Microalbuminuria is usually the first symptom, followed by persistent proteinuria, a drop in estimated glomerular filtration rate (eGFR), and finally renal failure. For prognosis and treatment, early diagnosis is crucial and depends on regular monitoring of the urine albumin-to-creatinine ratio and eGFR in addition to KDIGO staging. To distinguish non-diabetic renal diseases, renal biopsies are only performed in unusual circumstances. Strict blood pressure and glucose control, suppression of the renin-angiotensin-aldosterone system, and dietary and exercise changes are the mainstays of management. SGLT2 inhibitors, GLP-1 receptor agonists, and new anti-inflammatory and anti-fibrotic medications are examples of emerging treatments that have encouraging Reno protective benefits. Despite improvements, DN remains a significant global health and financial burden, underscoring the necessity of early screening, individualized care, and ongoing research.

Keywords: Diabetic nephropathy, Diabetes mellitus, End-stage renal disease, Micro albuminuria, eGFR, RAAS, SGLT2 inhibitors, GLP-1 agonists, Reno protection.

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INTRODUCTION

About 10% of people worldwide suffer from diabetes mellitus (DM), a chronic metabolic disease that is widely acknowledged as a significant public health concern and contemporary epidemic [1-3]. Persistent hyperglycemia brought on by decreased insulin secretion, resistance to insulin action, or a combination of the two is its defining feature [4]. The illness is frequently linked to metabolic problems, such as dyslipidemia, elevated basal metabolic rate, and compromised antioxidant defense systems, which ultimately interfere with the metabolism of vital biomolecules [5,6]. Growing rates of obesity, urbanization, sedentary lifestyles, and high-calorie eating habits are all closely associated with the rising prevalence of DM worldwide [7,8]. According to projections, the global burden is expected to increase significantly over the next few decades [9].

Type 2 diabetes is the most common type of the disease and is often linked to progressive microvascular complications that impact the kidneys, peripheral nerves, and retina [10]. These issues raise morbidity, mortality, and medical costs while drastically lowering quality of life [11]. Numerous major consequences, such as heart disease, cerebrovascular illnesses, kidney failure, inflammation and immunological dysfunction, and obesity, have diabetes as their primary cause. Gender, age, and cultural background are important determinants in the development of DM and its consequences, according to epidemiological studies. Albumin is converted by Amador glucose adducts to glycated albumin, which is independently linked to diabetic problems. Increased blood glucose levels are caused by issues with insulin metabolism as well as dysfunctions in the metabolism of proteins, fats, and carbohydrates, which can result in long-term problems [12]. One of the most dangerous and prevalent long-term microvascular consequences of diabetes is diabetic nephropathy (DN), also known as diabetic glomerulosclerosis or Kimmelstiel–Wilson syndrome [13]. Renal glomeruli, podocytes, mesangial cells, and tubulointerstitial compartments are gradually damaged both structurally and functionally [14]. Since DN is now acknowledged as the primary cause of end-stage renal disease (ESRD) and chronic kidney disease (CKD) globally, its prevention, early detection, and therapeutic management are crucial clinical and research priorities [15]. Developing successful interventions that could postpone or stop renal decline in diabetic patients requires an understanding of its intricate pathophysiology.

EPIDEMIOLOGY

The prevalence of diabetes and its renal complications is rising alarmingly on a global scale. An estimated 589 million adults between the ages of 20 and 79 have diabetes, according to the most recent International Diabetes Federation. DIABETES Atlas (2024–2025). Projections show that the number will rise to 783 million by 2045, indicating a rapidly accelerating trend that surpasses earlier projections [16,17]. DN, one of the most common microvascular complications and a major cause of morbidity and healthcare costs, affects about 30–40% of people with diabetes [18,19]. At present, 40–44% of cases of ESRD worldwide are caused by diabetes [20,21].

Due to its high population density and quick demographic changes, Asia continues to be the most affect regions. Previous estimates put the no of diabetes cases in Asia at over 200 million in 2013 [22,23], but new surveillance indicates that the number is still rising, especially in South Asia. With a national prevalence of about 10.5% and an estimated 89.8 million adults with diabetes, India is one of the major contributors to the global burden of DN. Despite having relatively lowest body mass index thresholds, Asian populations are particularly vulnerable because of increased visceral adiposity, insulin resistance (IR), and

AQ1 inflammation. The increase in DN cases in younger age groups is being accelerated by rising rates if obesity, sedentary lifestyles, urbanization, and earlier disease onset. Importantly, significant socioeconomic difference are also reflected in the epidemiological pattern of DN with low and middle income nations having poorer clinical outcomes and disproportionately higher rates of disease progression because they have less access to screening biomarkers renal replacement therapy and new treatment this disparity leads to a delayed diagnosis frequently at an irreversible stage of renal damage furthermore it is now known that a significant comorbidity clusters that increase that the DN and speeds up renal decline is the increasing prevalence of metabolic syndrome non-alcoholic fatty liver disease and hypertension [24,25]. The earlier age at which type 2 diabetes first manifests in Asian and Middle Eastern populations indicates that in the absence of effective preventive and intervention measure the burden of DN may increase in the future.

Collectively, these evolving epidemiological trends highlight DN as not only a clinical complication of diabetes but also a growing global health crisis. To lessen the long-term renal, cardiovascular, and socioeconomic effects of this condition, more aggressive screening, early diagnostic biomarkers, and easily accessible therapeutic approaches are desperately needed due to the condition's rising prevalence, younger age of onset, and growing disparities in outcomes.

Clinical presentation

The primary indicators of DN are elevated blood pressure (hypertension) and body fluid retention. Proteinuria and renal artery arteriosclerosis are additional complications. DN has no symptoms in its early stages, but as it worsens and the kidneys fail, it may result in the excretion of large amounts of protein in the urine. Edema is swelling, usually around the eyes in the morning. Anorexia (lack of appetite), morning sickness, nausea and vomiting, malaise (general unwell feeling), weakness, paleness, anemia, lethargy, headache, frequent hiccups, and widespread itching can all develop later. Other symptoms include ankle and thigh swelling, the need to use the restroom more often at night, and excessive or frothy foaming of the urine caused by proteinuria. The first abnormality in the lab is a positive microalbuminuria test. Glucose can also be detected by urine analysis, particularly if blood glucose control is inadequate. As renal disease progresses, blood and serum urea nitrogen levels may increase. Fluid filtration abnormalities and other issues with renal function are the result of glomerulosclerosis-induced renal failure [26]. Patients with advanced stages of nephropathy were more likely to have clinical indications, including pedal edema and puffy face. Although these indicators are non-specific, their presence should trigger an assessment for renal involvement. This study's link between HbA1c levels and CKD staging is consistent with other research and highlights the importance of using HbA1c as a prediction of renal problems as well as a marker of glycemic management [27].

PATHOPHYSIOLOGY

The onset and progression of DN are caused by a variety of factors, including an interaction between genetic predisposition, which creates the conditions for kidney damage, and hyperglycemia-induced metabolic and hemodynamic changes [27]. Hemodynamic factors influence the activation of numerous vasoactive systems, such as the endothelin and renin-angiotensin-aldosterone systems (RAAS). This leads to increased secretion of profibrotic cytokines and transforming growth factor 1 (TGF-1), which causes additional hemodynamic changes, such as increased intraglomerular and systemic pressure. A few signs of metabolic pathway involvement include aberrant polyol metabolism, increased protein kinase C (PKC) activity, and no enzymatic glycosylation. Increased secretion of inflammatory molecules, such as growth factors, metalloproteinase, and cytokines, has been linked to the development of DN in numerous studies [28,29]. Another important factor appears to be oxidative stress [30].

Hemodynamic pathway

The initial signs of glomerular hyperperfusion and hyperfiltration are brought on by decreased resistance in the afferent and efferent arterioles of the glomerulus. The afferent arteriole seems to have a greater resistance drop than the efferent arteriole. This defective auto-regulation has been linked to prostanoids, nitric oxide, TGF-1, vascular endothelial growth factor (VEGF; now officially known as VEGF-A), and the renin-angiotensin system (RAS), particularly angiotensin II. Albumin leakage from glomerular capillaries, excessive mesangial cell matrix synthesis, thickening of the glomerular basement membrane, and podocyte damage are all facilitated by early hemodynamic changes [31]. In addition, the increased mechanical strain brought on by these hemodynamic changes may result in the localized release of certain growth factors and cytokines [32,33]. Angiotensin II and endothelin are examples of vasoactive hormones that mediate changes in renal hemodynamics. Glomerular hypertension and hyperfiltration lead to the development of DN because renin-angiotensin blockers maintain kidney function and morphology. By reducing TGF-1 activation, the renin-angiotensin-aldosterone pathway is blocked, thereby counteracting the profibrotic effects of angiotensin II [34].

Metabolic pathway

Hyperglycemia and advanced glycosylation end product

Hyperglycemia is associated with basement membrane thickness, increased matrix synthesis, and mesangial cell proliferation and hypertrophy [35]. Mesangial cell expansion seems to be partially mediated by an increase in the mesangial cell glucose concentration because similar changes in mesangial function can be induced in a normal glucose milieu by overexpressing glucose transporters, such as GLUT1 and GLUT4, thereby increasing glucose entry into the cells [36]. Hyperglycemia may also enhance VEGF expression in podocytes [37]. That could greatly increase the permeability of blood vessels [38,39]. Three theories have been put forth to explain how tissue damage is facilitated by hyperglycemia: PKC activation, aldose reductase (AR) pathway acceleration, and advanced glycosylation end products are the outcomes of non-enzymatic glycosylation. All three pathways involve oxidative stress [40]. DKD is exacerbated by dyslipidemia, hyperglycemia, and IR. SGLT-1 and SGLT-2 are upregulated in the proximal tubule when there is an excess glucose load, increasing glucose and sodium reabsorption. This impairs tubuloglomerular feedback and reduces sodium transport to the distal nephron, which disturbs normal glomerular hemodynamics [41].

Glycosylation

The glycosylation of tissue proteins contributes to the development of DN and other microvascular issues. A portion of the excess glucose in long-term hyperglycemia interacts with circulating proteins or free amino acids on tissue. This non-enzymatic process, which first produces reversible early glycosylation end products and then irreversible advanced glycosylation end products, affects the glomerular basement membrane and other matrix components in the glomerulus. These innovative products may influence the pathophysiology of DN by altering the levels of soluble signals, such as cytokines, hormones, and free radicals. People with diabetes, particularly those with renal failure, have higher levels of advanced glycosylation end products in their blood because they are typically excreted in the urine [40]. In the end, the tissue accumulates advanced glycosylation end products (partially due to collagen cross-linking), aggravating renal and microvascular issues [42].

PKC

One of the other theories explaining how hyperglycemia promotes the development of DN is the activation of PKC [43]. Specifically, the activation of this enzyme promotes glomerular hyperfiltration by increasing the release of vasodilatoryprostanoids [44]. By activating TGF-β1, PKC may increase the amount of extracellular matrix generated by mesangial cells. Oxidative stress and de novo diacylglycerol synthesis are important mechanisms by which hyperglycemia triggers PKC [45]. PKC activation through dual phosphorylation activates mitogen-activated protein kinases (MAPK). In reaction to external stimuli at conserved tyrosine and threonine residues. The coactivation

of PKC and MAPK in the presence of elevated glucose levels indicates a relationship between these two enzyme families [46].

AR pathway

The polyol pathway is considered to be part of the etiology of DN. Increased glucose flow via the sorbitol pathway, which leads to the accumulation of both sorbitol and fructose, is thought to be one of the main metabolic abnormalities associated with diabetes hyperglycemia [47]. The build-up of intracellular sorbitol caused by an increase in AR activity is one of the mechanisms associated with the development of long-term diabetes complications. In this way, glucose is reduced to sorbitol by AR and the oxidation of NADPH/NADP+. Sorbitol dehydrogenase then reduces NAD+ to NADH and oxidises sorbitol to fructose. Sorbitol oxidation raises NADH, which causes the cytoplasmic redox state to change quickly and increases the production of reactive oxygen species (ROS). In oxidatively challenged cells, reduced NADPH may hinder glutathione (GSH) reduction. Conversely, long-term hyperglycemia increases the generation of ROS and causes the polyol pathway to consume too much NADPH. This inhibits reduced GSH, an essential substrate for GSH-peroxidase-mediated cellular antioxidant activity, and ultimately results in a disruption of antioxidant properties. As a result, it is thought that the polyol pathway plays a major role in the production of ROS during the development of DN. This may result in or worsen intracellular oxidative stress because reduced GSH, a crucial ROS scavenger, regenerates with the aid of the cofactor NADPH [48].

Oxidative stress

High levels of oxidative stress, which impair the body's natural antioxidant defences and promote the generation of free radicals, are experienced by diabetics and lab animals as a result of persistent and chronic hyperglycemia. Increased production of free radicals has been suggested as a common pathway connecting a number of pathogenic mechanisms leading to diabetic vascular complications [49]. The Oxidative stress, which is defined as an excessive production of ROS that surpasses the body's antioxidative defences, has a significant impact on both the pathophysiology of diabetes and the development of diabetic complications, such as DN. In addition to directly damaging cellular macromolecules, such as DNA, proteins, and lipids, free radicals can also indirectly disrupt normal cellular function by triggering several pathways that result in the production of AGEs, polyol and hexosamine pathways, and protein kinases. In addition, low antioxidant bioavailability promotes oxidative stress in cells, which exacerbates cellular damage. ROS in renal cells causes mesangial cell proliferation, growth factor production, extracellular matrix formation, RAAS activation, and the development of the epithelial-mesenchymal transition [50,51]. Furthermore, there is evidence that antioxidants can effectively stop the upregulation of fibronectin and TGF-ß1 caused by high glucose. Revealed that high glucose and nuclear factor kappa B (NF-κB)-dependent monocyte chemoattractant protein (MC production is mediated by ROS, cause NF-κB activation. NF-nuclear transcription factor κB can initiate the transcription of genes associated with an inflammatory response. Numerous stimuli linked to cell stress, including cytokines, growth factors, and vasoactive substances, cause it [52]. Human and rat diabetic kidneys, as well as proximal tubular cells in the urine sediment of type 2 diabetes patients, have been shown to exhibit NF-kB activation and nuclear translocation [53-55].

Genetic susceptibility

The incidence and severity of DN seem to be significantly predicted by genotype [56]. If a patient has a parent or sibling with type 1 or type 2 diabetes, their risk of developing DN is greatly increased. The likelihood that the child would have overt proteinuria rose from 14% when neither parent had proteinuria to 23% when both parents had proteinuria and 46% when both parents had proteinuria [57-59]. Molecular genetics advancements have made it feasible to genotype single-nucleotide polymorphisms and investigate the loci causing DN in genome-wide association studies. When looking for susceptibility genes for microvascular complications of diabetes in Pima Indians, four loci on chromosomes 3, 7, 9, and 20 were discovered. Other loci have been found to be susceptibility genes for DN on chromosomes 7q21.3, 10p15.3, 14q23.1, and 18q22.3. The greatest risks seem to be associated with angiotensin converting enzyme (ACE), angiotensin II receptor, cytokines, proteins involved in lipid or glucose metabolism, and extracellular matrix proteins [60,61]. A study of more than 1,000 white patients with type 1 diabetes found a strong correlation between genetic variation in the ACE gene and the development of nephropathy [62].

DIAGNOSIS

Urine albumin levels that are initially mild but abnormal are referred to as microalbuminuria (persistence of albuminuria at levels between 30 and 299 mg), also known as early nephropathy. Overt nephropathy or macroalbuminuria (persistent albuminuria at a level of $300 mg/24 h) may be present when type 2 diabetes is diagnosed, but it develops gradually in type 1 diabetes. Patients who progress to macroalbuminuria have an increased risk of developing ESRD [63].

Examining for DN

Most screening guidelines recommend measuring the albumin/creatinine ratio (ACR; normal, 30 mg/g creatinine) using either random specimens or spot urine samples from the first morning. Over several months, an abnormal result is repeated once or twice more to ensure consistency. Dietary Adjustments in CKD Together with this, epidemiology is used to assess renal function. Researchers have collaboratively developed formulations for estimated glomerular filtration rate (eGFR) to stage CKD. Screening typically starts 5 years after type 2 diabetes is diagnosed. Following the onset of diabetes type 1. Another option is to use timed collections, which average out variations in albumin excretion over the course of the day (normal, 20 g/min) [64,65].

Diagnostic evaluation of CKD using the KDIGO eGFR–ACR classification and risk-based stratification

The KDIGO classification, which combines ACR and eGFR, is used to diagnose CKD. According to the CKD Prognosis Consortium meta-analysis, risk increases gradually from G1-A1 to G5 with increasing hazard ratios for myocardial infarction, stroke, cardiovascular mortality, heart failure, kidney failure, and all-cause mortality. Cases with a rapid decline in glomerular filtration rate (GFR), heavy or inexplicable proteinuria, hematuria with casts, suspected autoimmune or glomerular disease, or a discrepancy between eGFR/ACR staging and clinical findings are all candidates for renal biopsy.

Renal biopsy

Renal biopsies are frequently used to confirm DN, a topic of much debate. When a patient has a history of diabetes or retinopathy, many nephrologists decide not to biopsy them. GFR decline over a 10-year period, proteinuria development at that time, and no active urine sediment. A study with 393 people with type 2 diabetes in Italy made this point. In comparison to centers with a restricted biopsy policy, those with an unrestricted biopsy strategy had a lower rate of finding an underlying glomerulonephritis (33% vs. 57%). A greater proportion of patients had glomerulonephritis rather than diabetic glomerulosclerosis as a result of the lax policy [67]. For some patients with CKD, renal biopsy is not always necessary. Rather, when the clinical presentation is unusual or the underlying etiology is still unknown, biopsy is advised by the most recent nephrology literature and KDIGO guidelines. A sharp drop in GFR, heavy or nephrotic-range proteinuria that cannot be explained, active urine sediment with hematuria or red blood cell casts, suspected autoimmune or glomerular disease, and significant albuminuria in diabetic patients without diabetic retinopathy are some specific indicators. Histopathological analysis of renal tissue is crucial in these situations to make an accurate diagnosis and direct treatment tailored to the patient's condition, ultimately improving management and patient care [68].

TREATMENT

Delaying the progression of DN requires effective management of metabolic and hemodynamic issues. In particular, this means that blood glucose levels will be sufficiently reduced and hypertension will be under control. The preference for certain antihypertensives is supported by studies that demonstrate reductions in proteinuria, preservation of GFR, or both.

Glycemic control

Glycemic control can lessen the microvascular effects of diabetes. According to the DCCT trial, macrophages mediate DN [69,70]. The accumulation of kidney macrophages is associated with the severity of glomerulosclerosis in humans [71]. Interstitial macrophage accumulation is closely associated with proteinuria, interstitial fibrosis, and a decrease in GFR [72]. The role of lymphocytes is less understood. An increased number of circulating activated T-cells is associated with DN. In addition to lowering blood sugar, some medications may have other beneficial effects. PPAR-inhibitors, such as pioglitazone and rosiglitazone, have demonstrated anti-inflammatory and antifibrotic effects in the kidneys of diabetic rats [73-76].

Antihypertensive and antidiabetic medications that reduce albuminuria and help preserve GFR remain the cornerstone of therapy, supported by several clinical trials

Delaying the progression of DN requires a comprehensive management strategy that targets hemodynamic and metabolic factors. Strict blood pressure control and optimal glycemic control are essential components of this approach. RAS inhibitors, such as ACE inhibitors and ARBs, are effective in lowering proteinuria and slowing the decline in GFR in patients with diabetic kidney disease (DN), according to strong clinical evidence. Effective glycemic control reduces diabetic microvascular injury and is strongly associated with better results [77].

According to recent studies, inflammation mediated by macrophages is crucial to the development and course of DN. Higher levels of glomerulosclerosis, interstitial fibrosis, proteinuria, and decreased GFR are linked to increased macrophage infiltration in the kidney. Experimental and clinical research citing the role of inflammatory cells in the development of disease supports these conclusions [78].

Furthermore, some medications that lower blood sugar also have renoprotective effects. In experimental models of DN, peroxisome proliferator-activated receptor gamma (PPAR-γ) agonists, such as pioglitazone and rosiglitazone, have shown antifibrotic and anti-inflammatory effects, potentially reducing renal inflammation and structural damage. Recent guidelines also highlight the kidney-protective qualities of other novel drugs, such as SGLT2 inhibitors and GLP-1 receptor agonists, in individuals with diabetes and CKD [79].

Antihypertensive therapy in DN

A key component of managing DN is maintaining optimal systemic blood pressure control because hypertension greatly speeds up the deterioration of renal function. According to current clinical guidelines, most patients should aim for a blood pressure target of ≤140/90 mmHg; however, those with macroalbuminuria should aim for a more stringent target of ≤130/80 mmHg, as tighter control has been demonstrated to slow the progression of CKD and lower cardiovascular risk [80].

RAS blockade remains the first-line antihypertensive treatment for DN due to the pleiotropic renoprotective effects of ACE inhibitors and ARBs that extend beyond blood pressure control. Both ACE inhibitors, such as captopril, and angiotensin II receptor blockers (ARBs), such as losartan and irbesartan, provide significant benefits by decreasing albuminuria, lowering intraglomerular pressure, and slowing the decline in GFR. Large, landmark clinical trials have demonstrated that these agents dramatically reduce the risk of ESRD and the doubling of serum creatinine levels. These effects are independent of their antihypertensive action, highlighting their important role in modifying the progression of DN [81,82]. When combined with ACE inhibitors or ARBs, mineralocorticoid receptor antagonists, such as spironolactone, further reduce proteinuria. However, the risk of hyperkalemia limits their usefulness, especially in patients with decreased GFR; therefore, careful monitoring of serum potassium is crucial [83]. Due to their additive antiproteinuric effects, non-dihydropyridine calcium channel blockers (NDCCBs), such as diltiazem and verapamil, may be helpful in patients who still have albuminuria despite optimal RAS blockade [84].

By increasing the antihypertensive and antiproteinuric effects of RAS blockers, diuretics play a crucial but supportive role. While loop diuretics work better in moderate to advanced renal impairment, where sodium retention and volume overload are more noticeable, thiazide diuretics are preferred in the early stages of CKD [83]. Diuretics play a supportive but important role by enhancing the antihypertensive and antiproteinuric efficacy of RAS blockers. Thiazide diuretics are preferred in the early stages of CKD, whereas loop diuretics are more effective in moderate to advanced renal impairment, where sodium retention and volume overload are more pronounced. Thiazide diuretics were favored in earlier stages of CKD, while loop diuretics were more frequently prescribed in advanced CKD with volume overload, according to a large retrospective cohort study assessing diuretic classes in CKD stages 3–4. Although neither type was found to be independently linked to progression, the study found that the differential use is indicative of the severity of the underlying disease and clinical indications for volume management. The use of loop diuretics was associated with increased mortality and hospitalization for cardiorenal events, whereas thiazide diuretics did not exhibit these associations, according to a recent study on patients with stage 3–5 CKD. This suggests that loop diuretics are useful in more advanced disease requiring potent diuresis, while thiazides are safer in earlier stages of CKD [85].

BIOMARKERS

Biomarkers play a critical role in the early detection and management of DN, a common and severe complication of diabetes characterized by progressive kidney damage. Traditional markers, such as albuminuria and serum creatinine, although widely used, have limitations in sensitivity and may not accurately reflect early renal injury. Consequently, research has focused on identifying novel biomarkers, including inflammatory cytokines, urinary proteins, such as neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), and genetic markers, which demonstrate greater potential for early diagnosis and monitoring disease progression. These biomarkers can facilitate personalized treatment strategies and improve clinical outcomes by enabling timely intervention before significant kidney function decline occurs [86]. The importance of tubular injury biomarkers in the early diagnosis of DN, even before the onset of significant albuminuria, has been highlighted by recent research. Researchers assessed serum cystatin-C, serum and urine NGAL, urinary KIM-1, and urinary N-acetyl-β-D-glucosaminidase in type-2 diabetic patients classified into normoalbuminuric and microalbuminuric groups in a clinical cross-sectional study published in the International Journal of Current Pharmaceutical Review and Research (IJCPR). In contrast to UACR (AUC 0.82) and cystatin-C (AUC 0.79), their results showed that serum NGAL had the highest diagnostic accuracy for predicting early DN, with an AUC of 0.85 [87].

Gene and cell-based therapy

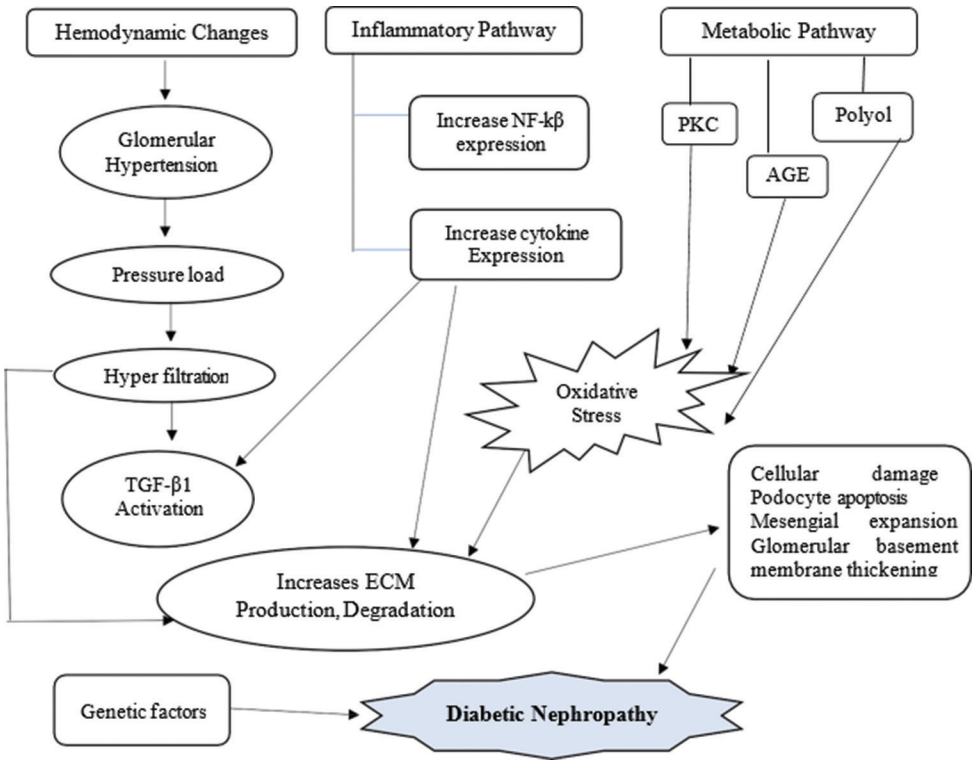
To promote the synthesis of a desired protein, a gene is inserted into cells as part of gene therapy. A carrier or vector, such as a modified adenovirus, is used to transport the gene to the nucleus, where the cellular machinery produces the protein that the gene codes for. Gene therapy that targets TGF-/SMAD signaling has the potential to lessen kidney damage in diabetic models. In the db/db mice model of type 2 diabetes, Ka *et al*. examined Smad7 gene therapy. Proteinuria, macrophage infiltration, inflammatory markers, podocyte damage, and renal fibrosis were all reduced as a result of the treatment because it prevented TGF-/SMAD and NF-B activation [88]. In db/db mice, it has been demonstrated that 155 HGF gene therapy increases renal

expression of SDF-1, which is accompanied by an increase in bone marrow-derived monocytes and macrophages with a larger proportion of M2 markers (anti-inflammatory phenotype). This was connected to a decrease in pro-inflammatory cytokines, are duction in histological damage, and podocyte preservation [89]. Progenitor cells, often known as stem cells, are multipotent cells that may self-renew and differentiate into specialized cells. They can be generally divided into two types: embryonic stem cells and adult stem cells. Adipose tissue, peripheral blood, and bone marrow are all sources of adult stem cells. Birth-related umbilical cord blood can also be used to collect stem cells. The following are some possible advantages of stem cell therapy for DN: (1) Replacing or rebuilding damaged cells, (2) controlling inflammation, (3) lowering oxidative stress, and (4) enhancing glycemia. A number of experimental investigations using stem cells to treat DN have been conducted (Table 1). Most research has shown that better pancreatic –cell function and insulin levels lower blood glucose levels, but some others haven't. This might have something to do with the type of cells used or the distribution mechanism. Some of these studies imply that a paracrine effect, as opposed to the regeneration or substitution of injured cells, is a more significant renoprotective mechanism. This is supported by findings of mesenchymal stem cell engraftment at low levels in the kidney and the generation of advantageous growth factors, antifibrotic agents, and antioxidants [90-92]. The three primary problems with cell-based therapy are: (1) consistency of generated cells

Table 1: KDIGO combined eGFR-ACR classification and risk stratification in chronic kidney disease [66]

KDIGO CKD Category	eGFR (mL/min/1.73 m^2)	Albumin-to-creatinine ratio (ACR) (mg/g)	Risk classification	Trend of hazard ratio for major complications (MI, HF, stroke, CV mortality, all-cause mortality, kidney failure, hospitalization, PAD)
G1-A1 (Low risk)	≥90	<30	Normal/no CKD	Reference values (ref) – baseline risk across all age groups.
G1-A2 (Moderately increased risk)	≥90	30–299	Mild CKD	Slight elevation in HR (≈1.1–1.6), mainly in older adults.
G1-A3 (High risk)	≥90	≥300	Proteinuric CKD	2–3×rise in HR for MI, HF, stroke, CV mortality, especially≥65 years
G2-A1 (Moderately increased risk)	60–89	<30	Mild CKD	HR~1.2–1.7 for CV outcomes and HF.
G2-A2 (High risk)	60–89	30–299	Proteinuric CKD	HR rises 1.6–2.3; stroke and HF risks increase more with age.
G2-A3 (Very high risk)	60–89	≥300	Proteinuric CKD	HR climbs to 3–6 for heart failure and kidney failure.
G3a-A1 (High risk)	45–59	<30	Moderate CKD	HR~2–3 for CV mortality and HF; hospitalization risk doubles
G3a-A2 (Very high risk)	45–59	30–299	Moderate CKD+ microalbuminuria	HR 3–5 for MI, CV death, and kidney failure
G3a-A3 (Extremely high risk)	45–59	≥300	Severe albuminuria	HR up to~6–8 for HF, stroke and kidney failure
G3b (A1-A3)	30–44	Any albuminuria	Severe CKD	Rapid rise in HR: MI 3–9×; HF 5–14×; kidney failure 6–46× (younger age HR increases more sharply)
G4 (A1-A3)	15–29	Any albuminuria	Advanced CKD	HF hazard ratio sometimes>100; stroke+CV mortality dramatically increased
G5/kidney failure	<15	Any albuminuria	Kidney failure	Highest HR across all outcomes – Kidney failure HR >600 and HF HR >100 in younger (<65) patients

HR: Heart rate, HF: Heart failure, CV: Cardiovascular, MI: Myocardial infarction, PAD: Peripheral artery disease, CKD: Chronic kidney disease



Flowchart 1: Pathogenesis of diabetic nephropathy

(phenotypic change happens with repeated passages), (2) cell delivery method (optimize tissue targeting and minimize passive trapping), and (3) engrafting and cell survival. Despite the aforementioned restrictions, research in stem cell and gene therapy is promising, but there have been no conclusive human trials to date. Additional research is also required to confirm that mesenchymal stem cells can treat DN without sacrificing any of its metabolic advantages.

CONCLUSION

In the complicated world of diabetes, a multifactorial approach is still the most sensible course of action because no single treatment can completely stop the development of DN. Strict glycemic control, single RAS inhibition for hypertension or albuminuria, and lipid management – ACE inhibitors for type 1 diabetes and statins for lowering cardiovascular risk – are the mainstays of present care. When necessary, second-line antihypertensives, such as NDCCBs and diuretics, may be taken into consideration. Mild salt and protein restriction are two examples of lifestyle changes that can provide extra benefits but necessitate close observation to ensure compliance. The key role of inflammation, especially macrophage-mediated pathways, has been brought to light by advances in our understanding of DN pathophysiology, indicating novel therapeutic options beyond traditional treatment. Although a number of therapies have improved surrogate indicators, such as albuminuria, there is still variable translation into long-term GFR preservation and ESRD prevention. Novel biomarkers, inflammatory pathway modification, and emerging treatments all show promise for future approaches, but thorough clinical testing is necessary to verify safety and effectiveness. All things considered, combining targeted experimental medicines with conventional therapy may offer the best chance to delay the course of DN.

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AUTHOR CONTRIBUTION

AD: Conceptualization of the review, literature search, data interpretation, writing the original draft, preparation of figures and tables, and manuscript revision. UV: Critical review and editing of the manuscript, validation, supervision, and final approval of the version to be published. All authors have read and approved the final manuscript.

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The authors declare that there are no conflicts of interest related to this manuscript.

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