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REVIEW ON THE IMPACT OF DIABETES ON KIDNEY DISEASE

Yasir Ansari [* 1], Akhilesh Patel [2], Kulbhushan Haldeniya [3], Rajesh Sharma [4], Mohd Haneef [5], Sourabh Kosey [6] and Ramesh Kumar [7]

Department of Pharmacy Practice [1, 2, 5, 6, 7], Department of Pharmacology [4], NIMS Institute of Pharmacy, NIMS University, Jaipur - 303121, Rajasthan, India.
Department of Surgical Gastroenterology & Liver Transplant [3], Nims University, Jaipur - 303121, Rajasthan, India.

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Correspondence to Author:
Yasir Ansari

Pharm D,
Department of Pharmacy Practice,
NIMS Institute of Pharmacy,
NIMS University, Jaipur - 303121,
Rajasthan, India.

E-mail: ansari.yasir2001@gmail.com

ABSTRACT: Diabetic kidney disease (DKD) is the main reason for end-stage renal disease on a global scale. About 40% of developing diabetic kidney disease, which is the most common cause of chronic kidney diseases worldwide. Although ESRD may be the most complication of diabetics, as a result of their physical health and any co-morbidities they may have, such as obesity, hypertension, dyslipidemia, intrarenal vascular disease, renal ischemia, or age-related nephron loss, One-third of people with type 1 diabetes and at least half of people with type 2 diabetes will eventually develop renal dysfunction. CKD is present and is severe. Glomerular hyperfiltration, falling GFR, and finally, ESRD are parts of the diabetic kidney disease natural history. Diabetes-related complications can lead to diabetic kidney disease. Disturbances in glucose metabolism, hypertension, dyslipidemia, develop kidney disease. Controlling blood sugar levels, blood pressure, and renin-angiotensin-aldosterone system blockage are all part of intensive therapy for diabetic patients; For diabetic kidney damage to be postponed or prevented, glycemic management is crucial. Several glucose-lowering drugs are on the market, but only a small percentage of them can be used safely in chronic kidney disease. The risk of kidney failure and cardiovascular events is significantly increased by diabetic renal disease, which has a significant global disease burden. There is still with current treatments. In order to find treatments that can halt the progression and lower risks, it is crucial to better understand the molecular pathways behind diabetic kidney disease. Which is subsequently accompanied by various metabolic, hemodynamic and inflammatory markers.

INTRODUCTION: Low estimated glomerular filtration rate (eGFR), albumin, or both are chronic kidney disease (CKD) symptoms [1]. Chronic kidney disease (CKD) and kidney failure are most frequently caused by diabetes mellitus, which is an epidemic that is getting worse. About 20–40% of people with diabetes develop diabetic nephropathy [2].

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Chronic kidney disease (CKD) is the most expensive of diabetes' long-term consequences and has the most negative effects on daily living. Individuals with CKD are more likely to experience negative health outcomes, such as frailty, a lower end-stage renal disease (ESRD), early mortality, and increasing end-organ damage at various sites.

Indeed, persons who have CKD are most affected by the increased mortality linked to both type 1 and type 2 diabetes. Individuals with CKD are more likely to experience. Negative health outcomes, such as frailty, lower end-stage renal disease (ESRD), early mortality, and increasing end-organ

damage at various sites. Indeed, persons who have CKD are most affected by the increased mortality linked to both type 1 and type 2 diabetes [3]. Due mostly to the rise in type 2 diabetes, the incidence and prevalence of diabetes mellitus have considerably increased globally. This rise in the number of persons getting diabetes has had a significant effect. Explain how diabetic kidney disease develops (DKD) [4]. In 1552 BC, the link between diabetes and kidney disease in people was first identified [5].

DKD's rising incidence is mirrored by diabetes's sharply rising prevalence over the world [6]. Adult diabetes prevalence increased in the United States, rising from 9.8% in the 1988–1994 era to 12.3% in the 2011–2012 decade [7].

The estimated global prevalence of diabetes in 2015 was 415 million; by 2040, it is expected to rise to 642 million, with a disproportionate increase in low- to middle-income nations [8] at each stage, it's critical to create cost-effective strategies [9]: prevention of obesity [10] screening for diabetes and its prevention in a population at risk [11].

Once diabetes manifests, glycemic control [12] controlling blood pressure (BP) after the onset of hypertension [13] Inhibition or blocking of the rennin-angiotensin-aldosterone system (RAAS) in people with diabetic CKD [14]. Control of other cardiovascular (CV) risk factors, such as controlling cholesterol levels in low-density lipoprotein (LDL-C) [15].

The worldwide obesity pandemic is what is causing the prevalence of diabetes to rise. In general, between 1980 and 2000, the predominance of In the United States, adult obesity increased dramatically, rising from 15% to 31%. By 2013–2014, 35% of men and 40% of women were overweight on an adjusted basis [16].

A large but unappreciated burden of sickness is diabetes-related renal damage. DKD-related deaths have become more frequent by 94% between 1990 and 2012. This sharp increase is one of the greatest ever recorded for reported chronic conditions. Notably, the majority of the elevated risk of mortality from all causes and cardiovascular disease (CVD) in people with diabetes is linked to the occurrence of DKD [17].

The Glomerular Filtration Rate does not Necessarily Fall in DKD Patients with Albuminuria: The most common clinical signs of DKD are albuminuria, which eventually develops into macroalbuminuria or overt proteinuria, microscopic hematuria, which only occurs in a limited percentage of patients, and a delayed improvement in renal function. DKD is traditionally divided into five stages.

Preclinical stages 1 and 2 are distinguished by an increase in GFR, normoalbuminuric (stage 1) or intermittent microalbuminuria (MA; stage 2), and normal blood pressure. Stage 3 is the beginning of the clinical stage, and it is distinguished and characterized by chronic MA, mild hypertension, and a stable or mildly declining GFR.

Macroalbuminuria, hypertension, and greater GFR reduction characterize stage 4 as compared to earlier stages. the latter stage of renal illness is stage 5. Recent epidemiological studies, however, especially for those with type 2 diabetes mellitus, evidence suggests that not all DKD patients fall into the aforementioned categories (DM). Not all people have proteinuria. Prior to the decrease of renal function associated with diabetes, in contrast to the traditional development of DKD outlined above [18]. [20].

In some patients, the change from MA to overt proteinuria may not take place until DKD progresses to ESRD. Perkins and others [21]. report an early decline in the majority of patients with just MA experience GFR. Additionally, nonproteinuric DKD a reduction in GFR without albuminuria is becoming a more well-known condition, particularly in type 2 diabetes [22, 26].

Renal insufficiency develops in persons with type 2 diabetes even when there is no albuminuria or retinopathy. Population-based research from Western nations found that over half of the people with a loss in kidney function either never developed proteinuria in type 2 diabetes or had no prior history of it [27].

A reduced correlation between nonproteinuric DKD and diabetic retinopathy was discovered than proteinuria DKD [28]. All of the findings point to the normoalbuminuric pathway for the progression of DKD. **Fig. 1** depicts a high-level overview of

DKD. **Table 1** Increased blood pressure, sustained reduction in glomerular filtration rate (GFR), increased cardiovascular events and cardiovascular event-associated mortality.

TABLE 1: DEFINITION OF THE ALBUMINURIA IN DIABETIC KIDNEY DISEASED

Normoalbuminuria	Daily urine albumin amount: <30 mg
Moderately increased albuminuria (Microalbuminuria)	Daily urine albumin amount: 30 mg–300 mg or Ratio of urine albumin over urine creatinine: 30–300
Severely increased albuminuria (Macroalbuminuria)	Daily urine albumin amount: >300 mg or The ratio of urine albumin over urine creatinine: >300

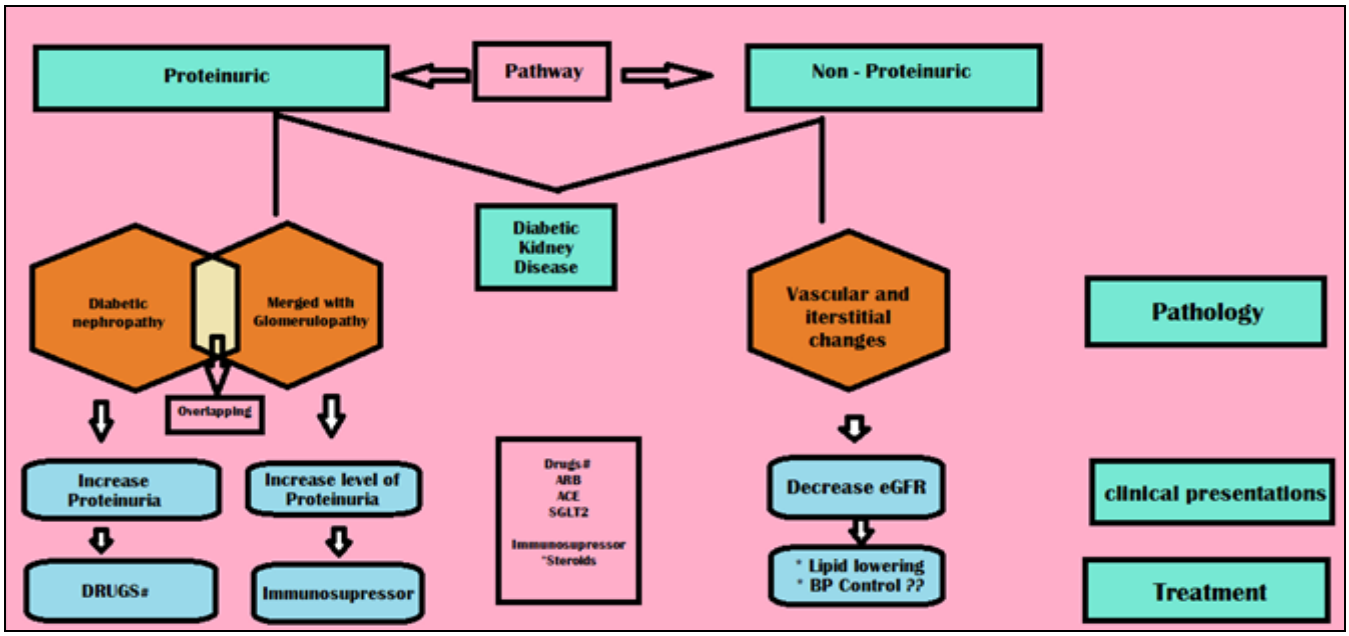

FIG. 1: DKD OVERVIEW. DKD STANDS FOR DIABETIC KIDNEY DISEASE; ACEI STANDS FOR ANGIOTENSIN-CONVERTING ENZYME INHIBITOR; ARB STANDS FOR ANGIOTENSIN II RECEPTOR BLOCKER; SGLT2 STANDS FOR SODIUM-GLUCOSE COTRANSPORTER 2; EGFR STANDS FOR ESTIMATED GLOMERULAR FILTRATION RATE; AND BP STANDS FOR BLOOD PRESSURE

Identification of DKD Patients at High Risk: DKD is a chronic, progressive disease that takes time to develop. In type 1 diabetes, the median period from the onset of overt proteinuria to the development of ESRD was 7 years. In the 1970s [29] and it is now 14 years [30]. At 30 years, the incidence of ESRD in type I diabetes in Finland is now 7.8% [31]. Many studies have found that the renal function of many properly managed individuals is either constant or develops slowly. The speed of the eGFR drop in three recent randomized interventional studies ranged from 0 to 4 mL/min per year [32-34]. Acute kidney injury is a major factor that may contribute to the progression of ESRD in diabetic patients (AKI) [35]. AKI increases the chance of developing advanced CKD whether it occurs once or repeatedly. In a cohort of 4,082 diabetic patients after that, a significant prospective investigation verified that AKI can predict y bad results. In diabetic patients, such as serum creatinine doubling or ESRD [36].

Increased Albuminuria: Increase excretion of albumin in the urine is a significant risk factor for the emergence and progression of renal disease. In people living with diabetes. It is characterized by increased excretion of albumin/g creatinine in the urine referred to as microalbuminuria (30–300 mg/g) or macroalbuminuria (>300 mg/g) [37].

Hyperglycemia: Hyperglycemia is regarded as one of the most important and independent risk factors for DKD [38]. It worsens renal function by altering the antioxidant system, resulting in increased formation of advanced glycation end products. The polyol pathway activation is also thought to be involved in the pathogenesis of DKD [39]. Variability in glycated hemoglobin (HbA1c) is linked to the development and progression of nephropathy in both type 1 and type 2 diabetes patients [40]. A similar finding was reported by the Italian multicenter study Renal Insufficiency and Cardiovascular Events (RIACE) [41].

Evidence from randomized controlled trials found that intensive glucose control was beneficial in both delaying the onset and preventing the progression of albuminuria in T2DM patients [42 43].

Hypertension: Hypertension is a major risk factor for diabetic nephropathy. A recent meta-analysis found that hypertension is significantly associated with the development of diabetic nephropathy [44]. Hypertension is associated with cardiovascular disease in children with CKD [45].

When compared to non-hypertensive patients, hypertensive patients have an odds ratio of 1.67 (95% CI: 13.1-2.14) [46]. This was confirmed by a population-based prospective study from China, which found that controlling hypertension can reduce the incidence of end-stage kidney failure by 23% [47].

Dyslipidemia: Dyslipidemia is critical to the development and progression of DKD. The "lipid nephrotoxicity hypothesis" describes the effect of dyslipidemia on renal function impairment [48]. Dyslipidemia is characterized in diabetics by a decrease in high-density lipoprotein and an increase in triglycerides, low-density lipoprotein, and very-low-density lipoprotein [49].

Dyslipidemia contributes to the development of DKD by causing podocyte apoptosis, macrophage infiltration, and an increase in extracellular matrix production [50]. Hyperglycemia and insulin resistance may aggravate dyslipidemia in DKD patients [51]. Epidemiological evidence suggested a positive relationship between dyslipidemia and diabetic nephropathy. An epidemiological study of 581 T2DM patients looked at the relationship between lipoprotein and DKD and discovered a link. Lipoprotein levels were discovered to be directly related to the presence of DKD [52].

Obesity: Obesity and DKD have a strong link, according to the evidence [53]. The mechanism by which obesity causes DKD is unknown, but it is assumed that obesity causes glomerular injury, hypertrophy, and proteinuria [54 55]. Obesity was identified as a risk factor in the development of nephropathy in a Chinese study of 264 patients with confirmed DKD based on renal biopsy [56]. Furthermore, an investigation of the Look AHEAD randomized clinical trial's secondary data suggests that weight loss could be used in conjunction with other treatments to slow the progression of diabetic nephropathy in obese patients [57].

Smoking: Tobacco use is regarded as a separate risk factor in the development and progression of diabetic nephropathy. Smoking has a multifactorial role in the development of diabetic nephropathy, including oxidative stress, hyperlipidemia, deposition of advanced end glycation products, and glomerulosclerosis [58 59]. Evidence from a Finnish diabetic nephropathy study of 3613 type 1 DM patients found that smokers had a higher risk of albuminuria and end-stage renal disease than non-smokers [60]. The dose of smoking was found to increase the risk of diabetic nephropathy. A recent meta-analysis based on the pooling of nine cohort studies concluded that smokers with T2DM are at an increased risk of developing diabetic nephropathy.[61]

Pathophysiology of DKD: Hyperglycemia and hyper aminoacidemia, two conditions that encourage glomerular hyperfiltration and hyperperfusion are critical metabolic changes in early diabetes that alter kidney hemodynamics and promote inflammation and fibrosis [62].

Fig. 2 Systemic hypertension and obesity, as well as high transmitted systemic BP and glomerular enlargement, contribute to glomerular hyper-filtration in type 2 diabetes. A common consequence of early diabetes is glomerular hyperfiltration. Overall, 10%–40%, or up to 75%, of type 1 diabetes patients and up to 40% of type 2 diabetes patients exhibit it. Still unidentified are the processes causing diabetes-related glomerular hyperfiltration [63].

One possible explanation is increased sodium-glucose cotransporter 2 activity in the proximal tubules, which results in decreased sodium chloride and other solute delivery to the macula densa at the distal end of the tubule [64, 65]. While excessive local angiotensin II production at the efferent arteriole results in vasoconstriction, the tubule glomerular feedback may be reduced, causing the afferent arteriole to expand and increase glomerular perfusion. Hyperfiltration of the glomeruli and high intraglomerular pressure are the overall consequences [66, 67].

Fig. 3 Early diabetes causes significant metabolic alterations, including hyper aminoacidemia, which encourages glomerular hyperfiltration and hyper perfusion, and hyperglycemia, that affect kidney hemodynamics and encourage inflammation and fibrosis. In addition, vasoconstriction is caused by excessive local angiotensin II production at the efferent arteriole. High intraglomerular pressure and glomerular hyperfiltration are the main consequences of hyperfiltration [68].

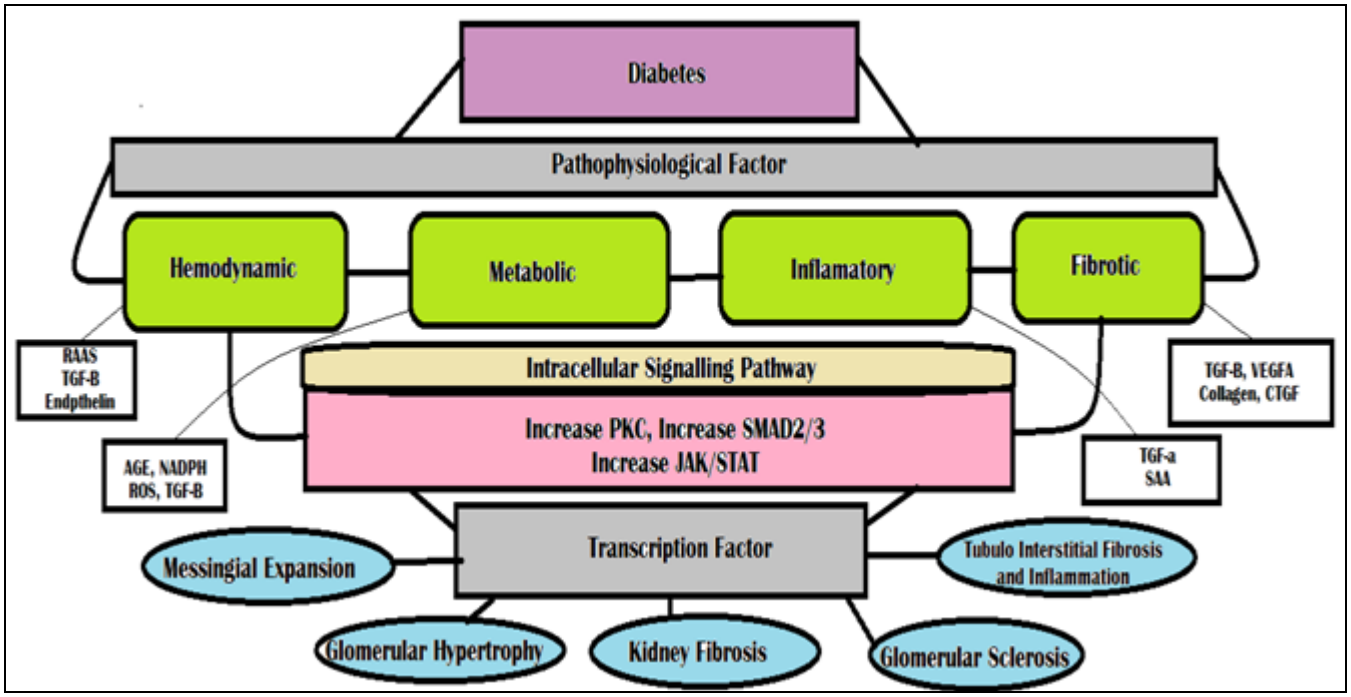

FIG. 2: THE DEVELOPMENT OF DIABETIC KIDNEY DISEASE INVOLVES A VARIETY OF ROUTES AND NETWORKS. CONNECTIVE TISSUE GROWTH FACTOR (CTGF), AGE (ADVANCED GLYCATION END PRODUCT); JAK-STAT STANDS FOR JANUS KINASE/SIGNAL TRANSDUCER AND ACTIVATOR OF TRANSCRIPTION; PKC STANDS FOR PROTEIN KINASE C; RAAS STANDS FOR THE RENIN-ANGIOTENSINALDOSTERONE SYSTEM; ROS STANDS FOR REACTIVE OXYGEN SPECIES; SAA STANDS FOR SERUM AMYLOID A; AND VASCULAR ENDOTHELIAL GROWTH FACTOR A IS REFERRED TO AS VEGF-A. *JAK/STAT SIGNALLING CAN REMAIN UNAFFECTED (↔)

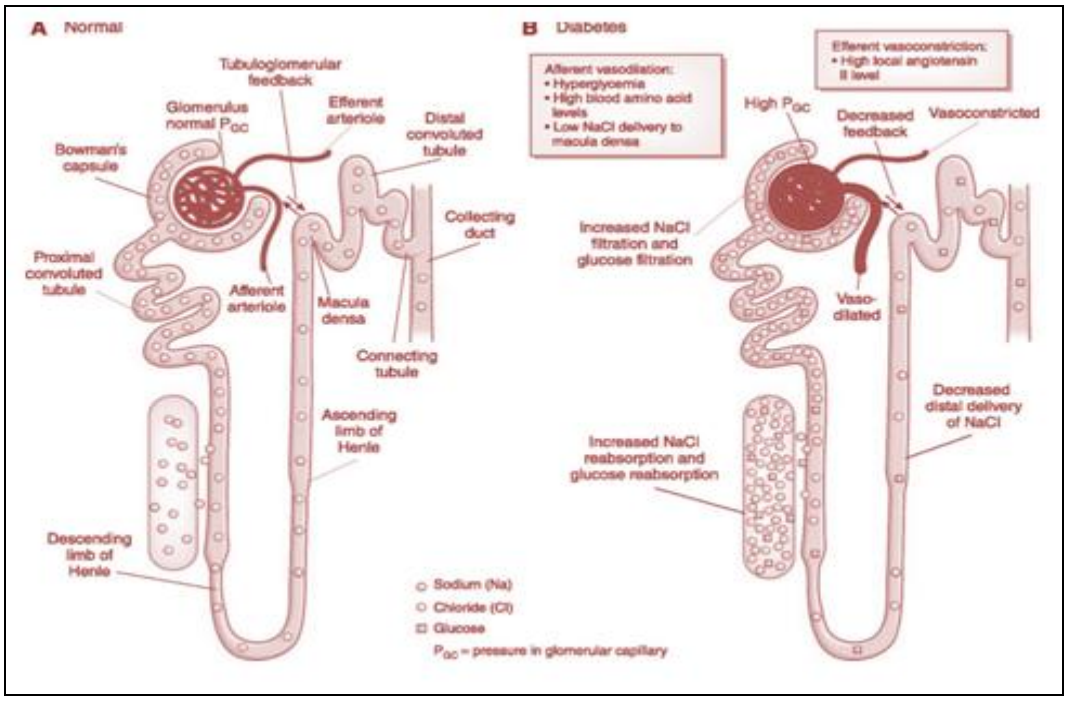

FIG. 3: THE RENAL HEMODYNAMICS OF NORMAL AND DIABETIC NEPHRONS ARE DIFFERENT

Diagnosis OF DKD: In addition to clinical characteristics including the duration of the patient's diabetes and the existence of diabetic retinopathy, Measurements of eGFR and albuminuria are used to make the clinical diagnosis of DKD.[69] DKD is diagnosed clinically by a sustained decline in eGFR < 60 ml/min per 1.73 m2 and/or a persistently high urine albumin-to-creatinine ratio of 30 mg/g [70]. Patients with DM1 should start getting screened for DKD every year starting five years after their diagnosis, and patients with DM2 should start getting screened every year at the time of their diagnosis. The occurrence of diabetic retinopathy in patients with albuminuria is a strong indicator of DKD. Urinary albumin-to-creatinine ratio testing is the optimum method for diagnosing albuminuria, and it should be done on a spot sample ideally in the morning [71]. The serum creatinine level is used to determine the eGFR. Although the Modification of Diet in Renal Disease equation is more commonly reported by clinical laboratories, the equation developed by the chronic kidney disease-Epidemiologic Prognosis Initiative is more precise, especially when eGFR readings are within the normal or near-normal range [72].

It takes two abnormal measures that are at least three months apart to confirm albuminuria or low eGFR. Other kidney disease reasons should be taken into consideration if symptoms that are not characteristic of DKD are present. Included in the list of unusual characteristics are the development of nephrotic or nephritic syndrome, fast commencement of low eGFR or rapidly dropping eGFR, an abrupt rise in albuminuria, resistant hypertension, symptoms or signs of another systemic disease, and >30% eGFR decline within 2-3 months after beginning a renin-angiotensin system inhibitor [73].

Treatment FOR DKD: For both DM1 and DM2, it is well known that maintaining long-term, intense glycemic control from the beginning of the course of diabetes prevents diabetic complications, including DKD [74, 75]. Intensive glucose management, however, has not been demonstrated to lower the risk of DKD development or enhance overall clinical outcomes after the beginning of complications or in long-term diabetes. In this population, aiming for low HbA1C (6%–6.9%) raised the risk of severe hypoglycemia but did not reduce the risk of cardiovascular (CV) or microvascular problems [76 77]. In addition, an examination of individuals with DM2 and early-stage CKD revealed that stringent glycemic control was associated with 30% and 40% higher risks for all-cause death and cardiovascular mortality, respectively, than conventional care [78]. Long-term research has supported the conclusion that intensive glycemic control carries a high does not lower the risk of CVD or all-cause mortality and increases the risk of hypoglycemia death (8–10 years). Although there was a slight reduction in the incidence of ESRD with strict glycemic control, the actual number of patients was very modest [79]. Intensive glycemic management beginning during early diabetes can prevent DKD, according to a stratified analysis, which revealed that the highest effect for preventing ESRD was shown in people without renal disease at the study entrance [80]. According to the American Diabetes Association, glycemia objectives should be customized for each patient's age, comorbidities, and expected lifespan. For patients with a shorter course of diabetes, a younger age, no comorbidities, and a longer life expectancy, more demanding objectives, such as HbA1C 6.5% greater, may be reasonable.

Contrarily, individuals with long-standing diabetes, advanced age, micro- and macrovascular problems, and short life expectancy are advised to adhere to less strict HbA1C8% objectives [81]. Similar to this, the Kidney Disease Improving Global Outcomes (KDIGO) recommendations and the Kidney Disease Outcomes Quality Initiative of the National Kidney Foundation. Suggest aiming for a goal HbA1c of roughly 7.0% to stop or slow the advancement of diabetes's microvascular adverse effects. However, treating to an HbA1c target of less than 7.0% is not recommended for patients at risk for hypoglycemia, such as those with diabetes and chronic kidney disease [82].

Beginning pharmacologic therapy was recommended by the Eighth Joint National Committee (JNC-8). for hypertension at a systolic blood pressure of fewer than 140 mmHg or a diastolic blood pressure of less than 90 mmHg, with treatment objectives lower than these levels. Initial antihypertensive therapy in the general hypertensive population, including those with diabetes, may consist of a calcium channel blocker,

ACE inhibitor, thiazide-type diuretic, or angiotensin receptor blocker (ARB). A thiazide diuretic or calcium channel blocker is advised by the JNC-8. as the first line of treatment for diabetic individuals of color. Regardless of their diabetes condition, people with CKD are advised to maintain the same BP goals. Either an ACE inhibitor or an ARB, either by itself or in conjunction with medication from any of the following groups, should be included in the pharmaceutical regimen for diabetic patients who have high levels of albuminuria [83]. Regardless of whether a patient has diabetes, the KDIGO guidelines advise using an ACE or an ARB and keeping their blood pressure at or below 130/80 mmHg [84]. There is clear proof that treating patients with macroalbuminuria reduces the development of DKD when combined with an ACE inhibitor or an ARB. By blocking the renin-angiotensin system [85]. Combination therapy (the administration of an ACE inhibitor and an ARB simultaneously) does not have any clinical advantages and raises the risk of major side effects, especially hyperkalemia and AKI [86 87]. The Systolic BP Intervention Trial results have cast doubt on target blood pressure objectives that have been suggested by the JNC-8's loosened guidelines (SPRINT). 9361 non-diabetic patients with high CV risk and hypertension were involved in the SPRINT study. The systolic blood pressure goals for participants were either intense (120 mmHg) or standard (140 mmHg).

After a median of 3.26 years, the study's early termination was due to a reduction of 25% and 27%, respectively, in the rates of the primary endpoint (myocardial infarction, acute coronary syndrome, stroke, heart failure, or death from CV causes) and all-cause mortality in the intervention group. The group receiving intensive treatment compared to the group receiving the standard regimen. These findings persisted in subgroups that had been previously established based on baseline systolic blood pressure levels, CKD stage, age >75, sex, race, and prior CVD [88, 89].

The risk of nonfatal myocardial infarction, nonfatal stroke, and mortality from any cause was not significantly different when the identical systolic blood pressure objectives were met (120 versus 140 mmHg). A CV cause, or death from any cause, according to 4733 individuals took part in the Diabetes and Action to Control Cardiovascular Risk (ACCORD) Trial. greater risk of cardiovascular events in diabetic people [90]. The ACCORD Trial may have been because of the much-reduced rates of CV morbidity and mortality; the study was underpowered to detect between-group differences. Anticipated, which is one reason for this inconsistent finding. However, rigorous BP treatment did not lower the incidence of ESRD, result in a 50% drop in eGFR, or result in a 30% decline in eGFR to a value of less than 60 ml/min per 1.73 m2 in the SPRINT participants who had CKD at study entrance. Additionally, the intensive therapy group saw more hospitalizations or ER visits due to AKI than the conventional regimen group (4.4% versus 2.6%; hazard ratio, 1.71) [91, 92]. Similar to this, the ACCORD Trial found evidence that suggests stringent BP control may have a deleterious impact on renal function. Even among participants with normal kidney function at baseline, the proportion of patients with an in the group receiving intense therapy, eGFR of 52 in the group receiving intensive therapy vs. 99 in the group receiving 30 ml/min per 1.73 m2 significantly quadrupled. The control group). control group; P = 0.001) [93].

New Treatments and Methods: There is still a sizable residual risk for DKD despite current methods for managing diabetes and hypertension, including the use of ACE inhibitors and ARB. The discovery of novel drugs that target mechanisms such as glomerular hyperfiltration, inflammation, and fibrosis has been a prominent emphasis. A protein kinase C-inhibitor called ruboxistaurin is one of the treatments that Has shown potential [94]. Specifically targeting Janus kinase 1 and Janus kinase 2, baricitinib [95] Anti-inflammatory and antifibrotic drug pentoxifylline [96]. A selective endothelin called atrasentan. antagonistic to the receptor [97, 98].

Along with finerenone, a highly specific nonsteroidal mineralocorticoid receptor antagonist [99] **Table 2.** S. Cr is expressed as milligrams per deciliter. The milligrams per gramme of protein to creatinine ratio is used. In milliliters per minute per 1.73 m2, eGFR is measured. UAE is measured in milligrams daily. In UACR, milligrams per gramme are used. Protein Kinase C, or PKC DM2, type 2 diabetic mellitus; AGE, advance glycation

end product; PYR-311, pyridoxamine-311; Pyridoxin (pyridoxamine dihydrochloride) has been shown to be safe and effective in treating subjects with nephropathy brought on by type 2 diabetes in Phase 3 Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study known as PIONEER. Hypertension, or HTN; serum creatinine (SCr); UAE, urinary albumin excretion; JAK1/2, Janus kinases 1/2; Influence of Pentoxifylline on Renal Function as well as Urinary Albumin Excretion in Diabetic Kidney Disease Patients; Reducing Residual Albuminuria using AtRasentan in Subjects with Diabetes and Nephropathy A Phase 2b, Retrospective, Endothelin A, ETA, and the urine albumin-to-creatinine ratio are all used in the randomized, double-blind, placebo-controlled trial known as RADAR/JAPAN. A Randomized, Multicounty, Multicenter, Double-Blind, Comparative, Placebo-Controlled Study to Evaluate the Impact of Atrasentan on Renal Outcomes in Patients With Type 2 Diabetes and Nephropathy; DM1, or type 1 diabetic mellitus; PERL, or Antihypertensive drugs Pilot Study to Prevent GFR Decline: A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Trial (ARTS-DN) was conducted to evaluate the safety

TABLE 2: NOVEL DIABETES-RELATED KIDNEY DISEASE TREATMENT

Title of the Study	Drug/Intervention Trials	Research Participants	Outcomes
Tuttle and others, 2005 (68)	Ruboxistaurin (PKC-inhibitor)	Macralbuminuria (DM2)	albuminuria was reduced, and kidney function was stabilized.
Pioneer (81)	PYR-311 (anti-AGE prescription)	DM2, HTN, 1.3 SCr, 3.0 mg/dl, and protein to creatinine ratio of 1200 mg/g	Halted
Predian (70)	Pentoxifylline (anti-inflammatory, antifibrotic effect)	DM2, eGFR = 15 to 60 ml/min per 1.73, and UAE > 300 mg/24 h	eGFR reduced 4.3 ml/min per 1.73 m2 quicker in the pentoxifylline group than in the control group, with an average albuminuria difference of 21%.
Baricitinib Safety and Efficacy in Participants with Diabetic Kidney Disease: A Clinical Study (69)	JAK1/2 antagonist baricitinib	macroalbuminuria, DM2, with eGFR between 20 to 75 ml/min per 1.73 m	In the highest therapy group, albuminuria decreased by 40% while eGFR was unaffected.
Both radar and radar/Japan (71)	Atrasentan (ETA)	DM2, eGFR = 30 of between 75 ml/min/ 1.73 m2, as well as UACR = 300 to 3500 mg/g	Improved albuminuria by 35%
SONAR, ongoing (72)	Atrasentan (ETA)	HTN, eGFR=15-90 ml/min for each and every 1.73 m2, with UACR >30 5000 mg/g	Ongoing
PERL, ongoing (82)	Allopurinol (xanthine oxidase)	eGFR with DM1 is 40-99 ml/min per 1.73 m2, whereas UAE are 18-5000 mg/d	Ongoing
ARTS-DN, 2015 (83)	Finerenone (steroid mineralocorticoid receptorantagonist)	DM2, UACR30 mg/g, with eGFR>30 ml/min with each 1.73 m2	There's no difference in eGFR, but albuminuria declines by 17% to 40% amount of the drug.

CONCLUSION: A clinical syndrome known as DKD includes persistent albuminuria, a sustained decline in GFR, high blood pressure, an increase in cardiovascular events, and mortality from these events. Compared to individuals without DM, dialysis patients with DM have a greater death rate. Recent research demonstrated that RAAS blockers, blood pressure control, blood glucose and lipid management, and smoking cessation are all effective multifactorial therapies that can dramatically improve the prognosis of individuals with type 2 DM with nephropathy. For the prevention and treatment of DKD, a wide range of novel drugs are being investigated, including SGLT2 inhibitors, GLP-1 analogues, DPP-4 inhibitors, thiazolidinedione, pentoxifylline, vitamin D analogue paricalcitol, pyridoxine, ruboxistaurin, solidified, JAK inhibitors, and nonsteroidal miner corticoid receptor antagonists. To assess the long-term outcomes in DKD patients,

additional studies focusing on the renal outcomes, not just changes in albuminuria, are required. One of the main causes of ESRD is DKD, which is also linked to increased cardiovascular morbidity and mortality. genetic and environmental aspects have been proposed as the risk factors that predict who experiences renal damage brought on by hyperglycemia. DKD results from the interaction of the metabolic and hemodynamic processes. Additionally, metabolic pathways in the diabetic kidney are engaged, causing AGE accumulation, PKC activation, the generation of renal polyols, and increased oxidative stress. Different cytokines and growth factors are activated by these aberrations. Mesangial expansion, GBM thickening, and glomerular sclerosis are the three pathways that ultimately result in renal histologic alterations in the glomeruli in diabetic nephropathy. At this time, the cornerstone of pharmacotherapy is the use of ACE inhibitors, ARBs, and glucose-lowering medications to block the RAAS. The most convincing proof of the size of the benefit that can be obtained from the Steno-2 trial is data from that study. putting in place a variety of risk factor reduction-focused strategies. For the prevention and treatment of DKD, more avant-garde methods incorporating pathophysiological mechanisms are required.

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