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Review Article

Comparative Effectiveness & Renoprotective Effects of Hypoglycemic Drugs for Type 2 Diabetes Mellitus

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Abstract

Type 2 Diabetes Mellitus (T2DM) is a huge burden on healthcare systems globally and it can lead to impaired kidney function, albuminuria, end-stage renal disease (ESRD). T2DM impact on the kidneys could results in diabetic nephropathy (DN) or diabetic kidney disease (DKD). It increases morbidity and mortality rate, therefore, decreases the quality of life. Present treatment protocol relies on lowering glucose levels, and strict blood pressure control by targeting blockade of the renin–angiotensin–aldosterone system. Such approaches might slow-down the decline in kidney function but many patients get end-stage kidney failure, despite optimal therapy. The need for new pharmacologic strategies for T2DM, that could prevent the development of DN and safeguard the kidneys, is rising. In this article, an overview of recent clinical data pertaining to novel therapeutic approaches for the management of DN is provided. Moreover, this review evaluates comparative effectiveness of hypoglycemic drugs like sodium-glucose cotransporter-2 inhibitors (SGLT2-i), glucagon-like peptide-1 receptor agonists (GLP1-RA), dipeptidyl peptidase-4 inhibitors (DPP4-i), and finerenone in treating T2DM and their renoprotective effects. This manuscript also highlights the need for selecting suitable drugs for a patient, as the optimal treatment significantly depends upon the patient-specific conditions.

Keywords: Diabetes mellitus, finerenone, glucagon-like peptide-1 receptor agonists (GLP1-RA), renoprotection; sodium-glucose cotransporter-2 inhibitors (SGLT2-i)

1. Introduction

Diabetes Mellitus (DM) is a widespread public health issue that carries a significant risk of microvascular and macrovascular consequences. A serious complication of diabetes called diabetic nephropathy (DN), also known as diabetic kidney disease (DKD), causes substantial harm to people all over the world(Cooper 2012). It manifests in 30% of diabetes patients, making it one of the most significant chronic complications of DM. There is an urgent need for novel therapeutic approaches targeted at arresting DN prognosis in diabetic patients.

The three phases of DN are: normoalbuminuria, microalbuminuria, and macroalbuminuria. Glomerular hyperfiltration can be regarded as a defining characteristic of its onset. As albuminuria develops, there is a corresponding decrease in the glomerular filtration rate (GFR) that correlates with the high blood pressure (BP), high glucose levels as well as high albumin excretion levels. However, other factors like gender, obesity, and hypertriglyceridemia can also lead to a decline in GFR(Porrini et al. 2015).

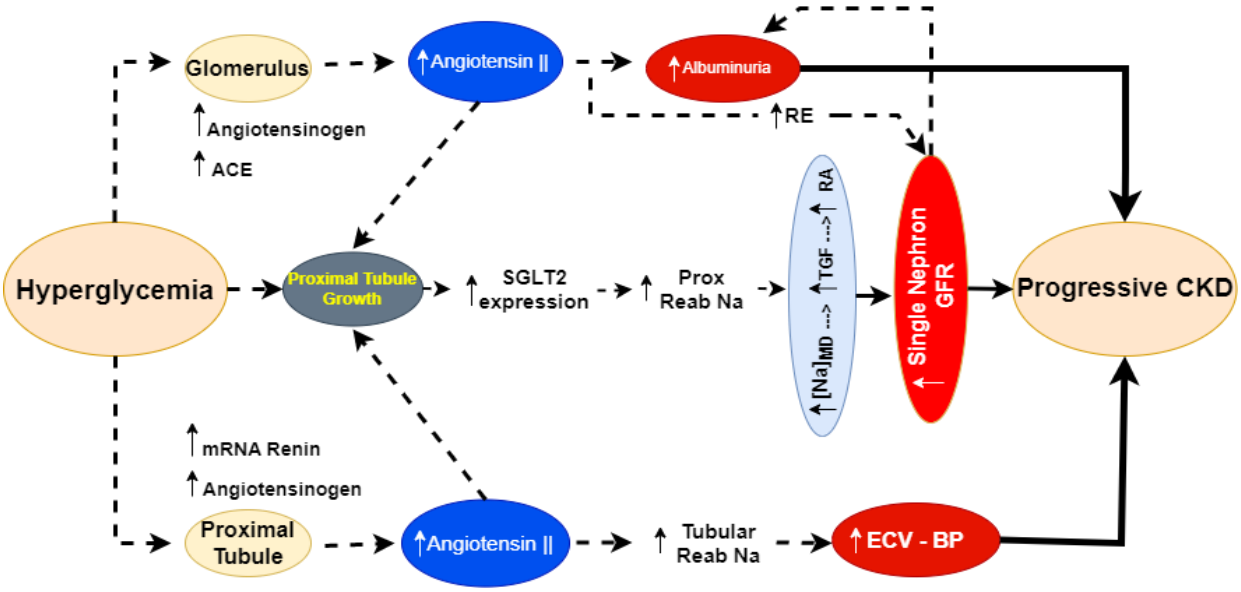

Figure 1: Underlying Mechanism of Diabetic Nephropathy

Reab; reabsorption, Prox; proximal, MD; macula densa, RA efferent arteriole resistance, BP; blood pressure, CKD; chronic kidney disease, EC; extracellular volume, TGF; tubulo-glomerular feedback, GFR; glomerular filtration rate.

1. Pathogenesis and the Course of Diabetic Nephropathy

The pathophysiology of DN is complex and is influenced by multiple factors. One of the main culprits is hyperglycemia, which leads to pro-inflammatory conditions, and advanced glycation end products (AGEs). These products result in cellular infiltration, up-regulation of adhesion molecules, elevated cytokine levels, increased metalloproteinase activity, and the generation of reactive oxygen species (ROS)(Hojs et al. 2016, Klessens et al. 2017). These factors contribute to renal inflammation, oxidative stress, and tissue damage, leading to a decline in GFR.

Pathophysiology of DN initiates (figure 1) with increased oxidative stress, intra-glomerular pressure, fibrotic changes and stimulation of the renin-angiotensin system (RAS). Moreover, inherent genetic susceptibility predisposes the patient to DN development(Martini et al. 2008). Furthermore, intra-renal immune cell infiltration and elevated levels of plasma inflammatory mediators (such as adhesion molecules and chemokines) have been seen in DN patients(Spranger et al. 2003). Glomerular hyperfiltration is the first sign of DN, and it fades away once early stage of renal impairment sets in. Mild systemic hypertension is present along with this and gets worse over time. Microalbuminuria (30-299 mg/24 h), which precedes macroalbuminuria (300 mg/24 h), is a symptom of early renal impairment caused by increased albumin excretion in the urine.

Another important stage in DN pathophysiology is the imbalance between efferent and afferent arteriolar pressures, which can impair the function and structure of the glomeruli (Klessens et al. 2017, Hojs et al. 2016, Muskiet et al. 2014). In diabetic patients, the afferent arteriole dilates, while the afferent arteriole constricts due to angiotensin II action. This alteration leads to increased intraglomerular pressure, which in turn causes glomerular hyperfiltration, glomerular hypertrophy, and eventually, glomerulosclerosis. Furthermore, insulin resistance, obesity, and dyslipidemia can impact

renal hemodynamics in DN. Insulin resistance is a common feature of T2DM and contributes to hyperglycemia, which plays a significant role in the development of DN. Obesity is known to increase the risk of developing T2DM and can also directly contribute to renal injury by increasing renal lipid accumulation, inflammation, and fibrosis. Dyslipidemia, or abnormal lipid levels in the blood, can also contribute to the progression of DN through various mechanisms, including direct toxic effects on renal cells, promoting inflammation, and increasing oxidative stress.

2. Treatment Strategies for DN Management

Treatment options for DN management includes, (a) monitoring BP (b) dietary caloric restriction alongside weight management (c) strict blood glucose control with the addition of angiotensin receptor blockers (ARBs) or angiotensin-converting enzyme(ACE) inhibitors to the pharmacologic regimen (d) avoiding nephrotoxic medications such as non-steroidal anti-inflammatory drugs (NSAIDs), contrast agents and antibiotics(Ritz et al. 1999, Atkins 2005) (e) statin therapy (f) abstaining from smoking, and (g) dietary protein prohibition(Epstein 2015, Rico-Mesa et al. 2020, Filippatos et al. 2021, Filippatos et al. 2022, Agarwal et al. 2022). The development of finerenone, a nonsteroidal selective mineralocorticoid receptor antagonist (MRA), was an important advancement for DN management. This medication has pharmacokinetic and clinical effects that vary from steroidal MRAs like eplerenone, and spironolactone. There are also potential new pharmacologic treatments that could halt the progression and development of DN and safeguard the kidneys(Mann et al. 2010).

3. Pharmacological Management of Diabetic Nephropathy

3.1. Classical Intervention for Diabetic Kidney Disease

Controlling BP with RAS blockade reduces proteinuria and successfully delays the progression of DN and Non Diabetic Nephropathy via local and/or systemic actions. It is critical to optimize glycemic control with antihyperglycemic medicines as well as insulin therapy. However, because of declining renal function, caution must be taken to adjust doses or avoiding certain drugs (Rojas and Gomes 2013, Bilous et al. 2012). Statins, particularly cerivastatin, simvastatin, and rosuvastatin can be used to treat DN because they decrease albuminuria, urinary endothelin, and even BP(Nikolic et al. 2013). Statins may have substantial nephroprotective effects that are dependent upon the length of therapy(Muskiet et al. 2015). Positive outcomes in terms of primary prevention were observed in different studies such as 'Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation (ADVANCE)' (De Galan et al. 2009), 'the Bergamo Nephrologic Diabetic Complications trial' (Remuzzi, Macia, and Ruggenenti 2006) and 'the Randomized Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP)' study(Haller et al. 2011).

3.2. Modified Treatment for Diabetic Kidney Disease

The development of novel glucose lowering drugs in recent years has greatly expanded the therapeutic choices for managing T2DM(Viberti and Wheeldon 2002, Persson et al. 2008). Some of these novel medications, including SGLT2 inhibitors and GLP-1RAs, not only help lower blood sugar levels but also decrease cardiovascular (CV) complications and maintain renal function(Patti et al. 2020). While insulin is

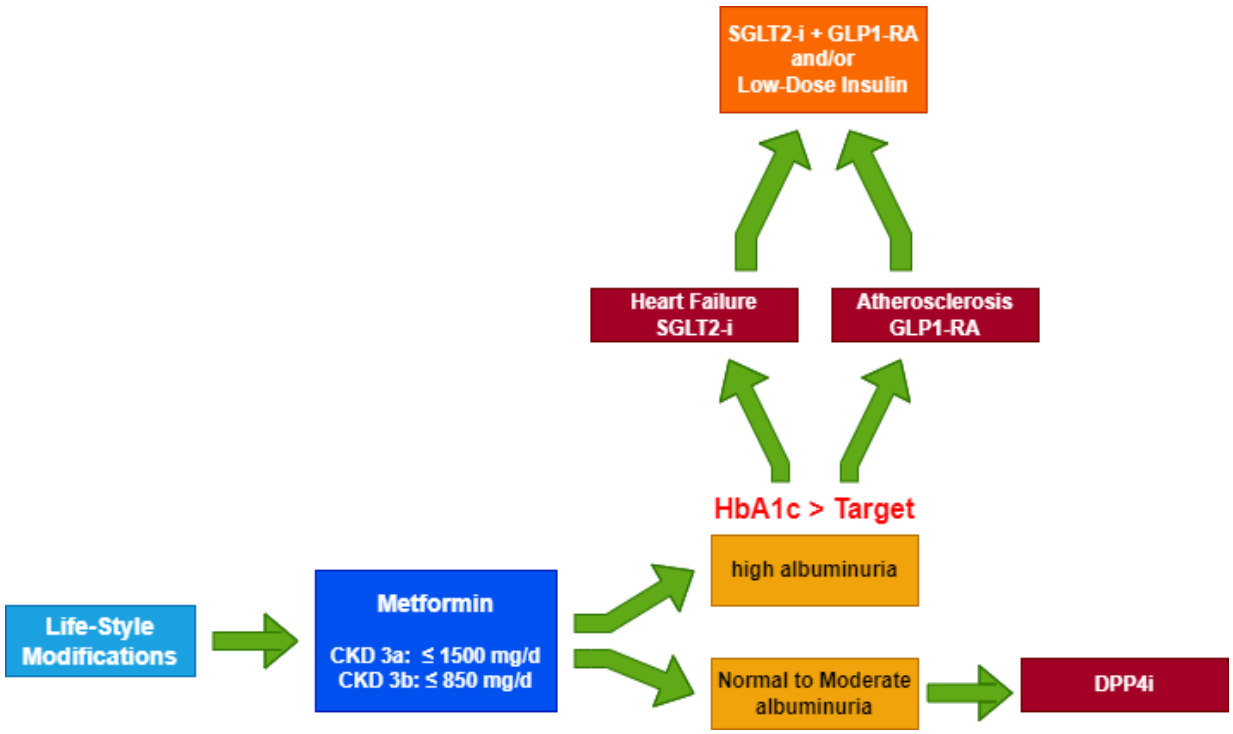

Figure 2: Novel Pharmacological Management of T2DM along with CKD.

the sole treatment available for people with type 1 diabetes mellitus (T1DM), several advanced anti-diabetic drugs approved for T2DM have demonstrated positive effects in T1DM as well. Few studies directly compare ACE inhibitors with ARBs in DN, but the present data suggest that the two classes have much similar beneficial effects on kidney outcomes. Likewise, with evidence based renoprotective studies, customizing individual diabetic management should be preferred as illustrated in figure 2. HbA_{1c} target level should be nearly 7%, according to the patients' condition.

Moving forward, it is crucial to continue researching new therapeutic options and strategies to further improve diabetes management. This may include identifying novel drug targets, optimizing existing treatments, and investigating in the potential benefits of combination therapies.

3.2.1. Sodium-Glucose Cotransporter 2 Inhibitors

The kidney plays vital roles in normal glucose homeostasis through use of glucose as metabolic fuel, gluconeogenesis, and reabsorption of most filtered glucose by the sodium-glucose cotransporters (SGLT1 and SGLT2 located in the luminal membrane of the proximal tubule. Most of the filtered glucose i.e., 80% to 90% is reabsorbed by the low-affinity, but high-capacity SGLT2 in the early S1 segment of the proximal convoluted tubule, while the remaining 10% to 20% is reabsorbed by the high-affinity but low-capacity SGLT1 in the more distal S2 /S3 segment.(Haller et al. 2011, Giglio et al. 2023). In patients with poorly controlled diabetes, the maximal renal glucose reabsorption capacity is enhanced compared to normal glucose tolerant individuals, likely due to up-regulation of SGLT2.

Sodium-Glucose Cotransporter 2 (SGLT2) inhibitors are the drugs that increase the urinary glucose excretion by inhibiting SGLT-2 activity in the proximal convoluted tubules; therefore, such inhibition of SGLT2 has been identified a preferable therapeutic agent in patients with T2DM. Subjects with low estimated glomerular filtration rate (eGFR) have a diminished hypoglycemic response because reabsorption of glucose at the proximal tubule level is directly related to blood glucose levels, limiting the amount that the glomerulus can filter(Kelly et al. 2019). Weight loss from glycosuria results from the loss of energy substrates, whereas water loss from diuresis results in volume depletion and lowering BP(Thomas and Cherney 2018). Secondary outcome analyses in clinical studies have demonstrated considerable renal protective effects and a delay in the progression of renal pathology (Wanner et al. 2016, Mosenzon, Wiviott, et al. 2019).

Clinical studies have shown that SGLT-2 inhibitors offer strong renal protection and can retard the progression of renal pathology by reducing blood glucose levels, improving renal hyperfiltration, ameliorating renal hypoxia, reducing proteinuria and mitigating weight, blood pressure, inflammation, uric acid, and oxidative stress. Empagliflozin, dapagliflozin, ertugliflozin, and canagliflozin are four representative SGLT2 inhibitors approved by the US Food and Drug Administration (FDA) and the European Medicines Agency for use as hypoglycemic drugs in patients with T2DM.

Several CV outcome studies in T2DM participants have indicated that the SGLT2 inhibitors empagliflozin (in Empagliflozin Cardiovascular Outcome Event Trial (EMPAREG OUTCOME)), canagliflozin (in Canagliflozin Cardiovascular Assessment Study (CANVAS))(Perkovic et al. 2018), and dapagliflozin (in Dapagliflozin Effect on Cardiovascular Events trial (DECLARE-TIMI 58))(Mosenzon et al. 2021) reduce the risk of chronic kidney disease (CKD) development. In addition, canagliflozin showed a significant reduction in the risk of CKD progression in CKD subjects (CANVAS programme)[(Perkovic et al. 2018) and dapagliflozin in CKD or non-diabetic CKD subjects (Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) and DECLARE-TIMI 58) (Mosenzon, Wiviott, et al. 2019, Mosenzon et al. 2021, Heerspink et al. 2020)

3.2.1.1. Canagliflozin

In the CANVAS program of randomized clinical trials, participants who received canagliflozin at a dose of 100 mg once daily and had albuminuric T2DM, CKD with an estimated glomerular filtration rate (eGFR) of 30 to 90 ml/min/1.73 m^2, and a urine albumin-creatinine ratio (uACR) between 30.0 and 500.0 mg/g, experienced a statistically significant 30% reduction in the primary endpoint ESKD, doubling serum of creatinine levels, or renal or cardiovascular-related death) compared to the untreated group ($p < 0.001$)[32]. Simultaneously, there was a statistically significant 32% reduction in the risk of ESKD ($p = 0.002$) and a 34% reduction in the doubling of creatinine levels and renal death ($p < 0.001$)(Perkovic et al. 2018).

3.2.1.2. Empagliflozin

In T2DM patients with cardiovascular disease the EMPA-REG OUTCOME test demonstrated that the increased urine albumin-to-creatinine ratio (UACR) after 12 weeks treatment was less than in the placebo group(Zinman et al. 2015). Moreover, after 16 weeks therapy, uACR and urinary albumin were apparently slower in the placebo group than in the T2DM patients with cardiovascular disease, and the same results were found in the subgroup analysis of 1517 Asian patients. Empagliflozin was a cause to delay the reduction in eGFR, proving that long-term or short-term use of empagliflozin is effective for albuminuria prevention (Kraus et

al. 2021, Wanner et al. 2016). Similarly, another study also reported that the risk of cardiovascular events or heart failure hospitalizations was lower in the placebo group compared with the empagliflozin group with or without diabetes, in subjects having recommended heart failure treatment, which could be good news for CVD with DKD(Anker et al. 2021).

3.2.1.3. Dapagliflozin

A decrease in cardiorenal outcomes (at least 40% prolong decline in eGFR > 60 ml/min/1.73 m², ESKD, or death from kidney or CV causes) was observed in the DECLARE-TIMI trial of 58 subjects with CKD and T2DM taking dapagliflozin compared to subjects with CKD but without diabetes: the group treated with dapagliflozin showed a significantly lower frequency of cardiorenal outcomes [hazard ratio; HR 0.76 (95% CI 0.67–0.87); p < 0.0001] and kidney-specific outcomes [HR 0.53 (95% CI 0.43–0.66); p< 0.0001] as compared to the placebo group; the dapagliflozin group also had a particular decreased frequency of composite cardiorenal outcome [HR 0.76 (95% CI 0.67–0.87); p < 0.0001] and kidney-specific outcomes [HR 0.53 (95% CI 0.43–0.66); p < 0.0001] with respect to the untreated group. The DAPA-CKD trial showed a 39% reduction in the primary endpoint (eGFR, ESKD, or renal or CV death) (p 0.001) compared to the placebo group in people with chronic renal failure with or without T2DM (67.5% and 32.5%, respectively) [53]. DAPA-CKD was the first research to indicate that an SGLT2 inhibitors lowered the risk of mortality in people with chronic renal failure and improved renal pathology outcome(Wheeler et al. 2021).

Canagliflozin was granted new indications by the FDA in 2019 to decrease the likelihood of ESRD, deterioration of kidney function, CV fatality, and hospitalization due to heart failure in patients diagnosed with both T2DM and CKD. The 'European Society of Cardiology' recommendations are found in the study (Zandecki et al.) called Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE)(Jardine et al. 2017). This trial compared canagliflozin 100 mg/day to a control group in diabetes patients with an eGFR of 3.0 to <9.0 ml/min/1.73 m²; the safety committee ended the study early when the superiority of canagliflozin was shown through analysis. Treatment via canagliflozin resulted in a 30% decline in the key outcome, which included the doubling of serum creatinine levels, a composite of end-stage kidney pathology, or CV renal death. Additional findings also demonstrated that canagliflozin use had good effects. These findings in a high-risk group of diabetics with renal impairment support secondary outcome observations in CV outcomes, and demonstrate the need of using SGLT2i in the treatment of T2DM with CKD, and CVD(Kristensen et al. 2019). Additionally, a meta-analysis using lixisenatide, liraglutide, exenatide, and semaglutide revealed a decline in the progression of macroalbuminuria and the risk of adverse effects of kidneys due to decreased proteinuria. This suggests that some GLP-1RAs may provide modest kidney benefits(Rizvi et al. 2022). Based on the findings of the CREDENCE, DECLARE–TIMI 5.8, and DAPA-CKD studies, canagliflozin would be beneficial for people with T2DM and diabetic nephropathy, albuminuria > 300 mg/day, and an eGFR ≥ 30 ml/min/1.73 m², while dapagliflozin would be beneficial for people with chronic renal failure and an eGFR ≥ 25 ml/min/1.73 m² who are at risk of CKD progression.

Dapagliflozin is supposed to reduce the risk of evolution of chronic kidney disease and heart failure regardless of albuminuria in all CKD subjects with or without type 2 diabetes, as well as reduce the chances of hypertensive heart failure (HHF) and CVD in heart patients with a

Table 1. Factors Responsible for Cardio-Metabolic-Renal Effects.

	Conditions		
	Cardiac Failure	**Atherosclerotic Effect**	**Diabetic Nephropathy**
Reduction in liver fat	✗	✓	✗
Antifibrotic	✓	✗	✓
Natriuresis	✓	✗	✓
Decline in body weight	✓	✓	✓
Glucose lowering	✗	✗	✓
Lowering of blood pressure	✓	✓	✓
Decrease in natriuretic peptides	✓	✗	✓
Reduction in extracellular matrix turnover	✓	✗	✓
Amelioration of intrarenal hypoxia	✗	✗	✓
Restoration of thetubuloglomerular feedback	✗	✗	✓
Anti-inflammation	✓	✓	✓
Decrease in energy demand	✓	✗	✓

low ejection fraction(Wheeler et al. 2021). Canagliflozin only reduced the risk of hospitalisation for heart failure and CVD in diabetic patients with albuminuria ≥ 300 mg/g(Perkovic et al. 2019).

The CREDENCE and DAPA-CKD studies found that dapagliflozin or canagliflozin cause a mean reduction eGFR by 3.7 ml/min/1.73 m² after three weeks and 4.0 ml/min/1.73 m² within two weeks. This decline is maintained and was consistent over the year, and it was lower with SGLT-2 inhibitors medications than in the untreated control group (Heerspink et al. 2020, Cherney et al. 2014). A drop in eGFR >10% was found in participants with advanced stages of chronic kidney failure with diminished diuresis who were treated with diuretics, however, this had no effect on renal or CV outcomes(Cherney et al. 2014).

3.2.2. Incretin-Based Therapies

GLP-1 is secreted at low tonic rates in the fasting and interprandial state from gut enteroendocrine L-cells. Circulating levels of GLP-1 rise abruptly within minutes of food intake. Earlier studies focused on its role as an incretin hormone, as it is responsible for the

approximately 70% amplification of insulin secretion in the context of nutrient ingestion especially glucose. This finding was proved by the fact that the glucoregulatory actions of this hormone also include suppression of glucagon secretion, decreased bowel motility, inhibition of gastric emptying rate and reduction in food intake and appetite, transduced by a single GLP-1R located in many organs including the kidney. In T2DM patients, GLP-1 level is reduced. GLP1-RA can aid GLP-1 to improve renal outcomes in type 2 diabetes. They improve renal tubular function and enhance diuresis and natriuresis. The effect of GLP-RAs on renal hemodynamics is attributed to the improved equilibrium between efferent vasoconstriction and afferent vasodilation (Asmar et al. 2015). The tubular transporter which mediates the natriuretic effects of GLP-1 is the Sodium Hydrogen Exchanger 3 (NHE3) also known as sodium–hydrogen antiporter, which is found on the edge of the brush of the proximal tubule. It is added to a formulation that also includes DPP-4 (Bankir et al. 2016). NHE3 is inhibited by the reduction of postprandial levels of glucose, glucagon or insulin(Pessoa et al. 2014), which cause inhibition and down-regulation of NHE3 and SGLT-1/SGLT-2(Rojas and Gomes 2013, Muskiet et al. 2014). Natriuretic and Diuretic actions of this hormone are assumed to be connected to the renal protection mechanism. GLP-RAs appear to cause glomerular hyperfiltration and an increase in GFR in physiological circumstances. It is feasible to directly impact the afferent arteriole by activating GLP-RAs in glomerular vascular smooth muscle cells. In addition to the endocrine pancreas, GLP-1 receptor mRNA has been discovered in the the gastrointestinal tract, peripheral and central nervous systems, the lungs, the kidneys, and the CV system (Sharma et al. 2018). As a result, it is reasonable to infer that, in addition to their hypoglycemic effects, these medications have antioxidant and anti-inflammatory qualities that may directly or indirectly improve renal function. GLP-1RAs include semaglutide, lixisenatide, dulaglutide and liraglutide, etc.

3.2.2.1. Lixisenatide

In the 'Evaluation of Lixisenatide in Acute Coronary Syndrome study (ELIXA)' T2DM patients, who had recently experienced an acute coronary event (unstable angina or myocardial infarction), were targeted. 25% of subjects in the lixisenatide group and 22% of subjects in the untreated group exhibited a reduction in eGFR(<6.0 ml/min/1.73 m²)(Pfeffer et al. 2015). In general, and after adjusting the baseline for albuminuria status, no statistically important differences in eGFR reduction were observed with lixisenatide treatment over placebo. However, there was a reduction in the onset of macroalbuminuria (HR 0.77; 95% CI: 0.62, 0.96; p = 0.0174), as well as a lower urinary UACR in patients taking lixisenatide with microalbuminuria (-21.10%, -42.25 to 0.04; p = 0.0502) or macroalbuminuria (-39.18%, -68.53 to −9.84, p = 0.0070)(Pfeffer et al. 2015).

3.2.2.2. Semaglutide

In a study as the 'Semaglutide and Cardiovascular Outcomes in subjects with T2DM Cardiovascular Outcome (SUSTAIN-6)', administration of semaglutide (subcutaneous) showed a reduction in the incidence of new cases of nephropathy or its progression (HR 0.64 (95% CI 0.46-0.88, p = 0.05). This was caused by a decrease in new-onset macroalbuminuria (0.973 with semaglutide 0.5 mg, 0.858 with semaglutide 1.0 mg). Post hoc analysis of SUSTAIN 1–5 and 7 revealed a 30% drop in albuminuria and significant regression to micro- or normoalbuminuria in all grades of albuminuria, The major goal of the 'Cardiovascular Safety of Oral Semaglutide in patients with T2DM (PIONEER-6)' study was to evaluate the cardiovascular safety of oral semaglutide; 26.9%

of the patients in the study had an eGFR of 60 mL/min/1.73 m². There were no statistically significant differences in eGFR drop and renal mortality; in Pioneer-5, participants with a moderate eGFR loss (30–59 ml/min/1.73 m²) were considered to be renally safe. (Mosenzon, Blicher, et al. 2019, Husain et al. 2019)

3.2.2.3. Exenatide

In 2017 'Exenatide Study of Cardiovascular Event Lowering (EXSCEL)', trial evaluating the CV safety of exenatide, was conducted. No significant change in the reduction of eGFR, RRT, or renal death was observed in the composite primary outcome of the first occurrence of CVD or nonfatal stroke. The exenatide group had a lower rate of macroalbuminuria (2.2%) than the untreated group (2.5%) (Holman et al. 2017).

A study demonstrating comparison of Dulaglutide with Insulin Glargine on Glycemic Control in individual with T2DM and Moderate or Severe CKD also looked at renal outcomes (AWARD-7). Patients with moderate to severe T2DM and CKD were given the maximal dose of insulin, an ARB or ACE inhibitor, and dulaglutide injected once per week. After 52 weeks of therapy, eGFR was greater with dulaglutide 1.5 mg (34.0ml/min/1.73 m²; p=0.005 versus insulin glargine) and dulaglutide 0.75 mg (3.3.8 ml/min/1.73 m²; p = 0.009 versus insulin glargine) versus insulin glargine (31.3 ml/min/1.73m²)(Tuttle et al. 2018). Treatment with Dulaglutide was related with a lower drop in eGFR in patients with microalbuminuria(Tuttle et al. 2018).

The renal outcomes, investigated in the 'Researching Cardiovascular Events with a Weekly Incretin in Diabetes (REWIND)' trial demonstrated a constant 30% drop or more in eGFR. A combination of these outcomes occurred in 17.1% of dulaglutide (1.5 mg) patients and 19.6% of patients who did not receive treatment (HR 0.85, 95% CI 0.77–0.93; p = 0.0004)(Gerstein et al. 2019). In a research study to see how semaglutide works compared to placebo in people with T2DM and CKD (FLO), the impact of semaglutide on the progression of renal impairment in patients with T2DM and CKD was examined. This trial showed relatively positive outcome with reference to renoprotection (Novo Nordisk 2022).

3.2.3. Dipeptidyl Peptidase-4 Inhibitors

In the pursuit of new drugs for DKD, the investigation of the degradation agent of GLP-1 is a crucial area of focus. DPP-4 is responsible for the degradation of GLP-1. DPP-4 inhibitors have the ability to elevate endogenous GLP-1 levels and safeguard renal function, even in the absence of GLP-1 involvement. As DPP-4 increases GLP-1 and Gastric inhibitory polypeptide levels, this can inhibit glucagon release while raising insulin secretion, decreasing stomach emptying, and decreasing blood glucose levels. DPP-4 inhibitors can minimize TNF-α levels, inhibit the immune response of malondialdehyde, and perform the role of an anti-oxidant and anti-inflammatory agent, thus it can delay glomerulosclerosis (Sun et al. 2012). In the kidney, inhibition of DPP-4 can leads to distal diuresis, but usually does not markedly affect renal hemodynamics(Sun et al. 2012). They are appropriate in patients with advanced T2DM and renal impairment. Furthermore, DPP-4 is abundantly expressed in the epithelial and endothelial tissue of the proximal renal tubules, and it interacts with extracellular matrix components (fibronectin and collagen)(Mosenzon et al. 2017). DPP-4 inhibitors reduce proteinuria levels and reduces renal fibrosis and podocyte damage in addition to glycemic control(Laakso et al. 2015). DPP-4 inhibitors include saxagliptin, linagliptin, sitagliptin and many more.

3.2.3.1. Saxagliptin

In a study called 'Saxagliptin Assessment of Vascular Outcomes Recorded in individuals with DM Thrombolysis in Myocardial Infarction (SAVOR TIMI 53)'(Sun et al. 2012), saxagliptin was linked with a decline in albuminuria level regardless of glucose control. There was no statistically significant difference during follow-up in eGFR or the prevalence of renal endpoints(Sun et al. 2012). Significant decreases in sitagliptin-associated albuminuria were observed in the 'Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS)' research on sitagliptin with no changes in eGFR(Cornel et al. 2016).

3.2.3.2. Linagliptin

The Cardiovascular and Renal Microvascular Outcome Study with Linagliptin (CARMELINA)' found that the medicine was cardiovascularly safe, with no significant differences in renal outcomes except slower progression of albuminuria compared to the placebo(Rosenstock et al. 2019). 'The Efficacy, Safety, and Modification of Albuminuria in T2DM Subjects with Renal Disease with Linagliptin (MARLINA-T2D)' experiment followed patients treated with linagliptin who had increased urine albumin excretion (albumin-to-creatinine ratio more than 30 mg/g). This medication improved glycemic management while having no statistically significant effect on albuminuria levels(Groop et al. 2017). The effect of DPP-4 in DN patients has been neutral, despite the fact that the medicines were determined to be renally safe (Rosenstock et al. 2019).

3.2.4. Mineralocorticoid Receptor Antagonist

Finerenone is a recently found mineralocorticoid receptor antagonist. There are two main phase three randomised controlled trials which observed the therapeutic effects of finerenone on the CV and renal systems in T2DM and CKD patients. These studies include, 'Finerenone: in minimizing Kidney Failure and Disease Progression in DKD(FIDELIO-DKD)'(Filippatos et al. 2021) and 'Finerenone in Reducing Cardiovascular Mortality and Morbidity in DKD (FIGARO-DKD)'(Filippatos et al. 2022). FIGARO-DKD and FIDELIO-DKD had a primary and secondary endpoint but were inverted (renal and CV endpoint, respectively, albeit with less significant CKD in the later trial). Finerenone has been demonstrated to have CV advantages both alone and in combination with GLP-1RAs or SGLT2 inhibitors(Agarwal et al. 2022). Furthermore, according to the meta-analysis of the FIGARO-DKD and FIDELIO-DKD trials, finerenone demonstrated a decrease in renal risk, ≥57% reduction in eGFR, and a reduction in the risk of irreversible renal damage or failure ; it also exhibited a decrease in CV risk by evaluating time to non-fatal stroke, hospitalization for heart failure and cardiovascular death(Agarwal et al. 2022).

3.2.5. Novel Lipid-Lowering Drugs

There are high levels of low-density lipoprotein-cholesterol(LDL-C), very low-density lipoprotein (VLDL), and lipoprotein a, as well as low levels of Apolipoprotein A1 (ApoA1) in CKD patients(Giglio et al. 2021). According to the recent guidelines for the treatment of dyslipidemia, CKD is a disease associated with a greater chances of atherosclerotic cardiovascular disease (ASCVD); the LDL-C target is less than 55 for secondary prevention or 70 mg/dl for primary prevention(Visseren et al. 2022). The treatment of dyslipidemia in CKD patients is still a challenge. Patients with less severe renal impairment appear to consistently benefit from hypolipidemic drugs/statins treatment in both primary and secondary prevention(Palmer et al. 2012); Although, despite the beneficial effect of hypolipidemic drugs, reduced renal function can lead to statin associated side effects, including myopathy. In patients with advanced

CKD, especially in patients with ESRD or even undergoing hemodialysis, statins have not exhibited the ability to minimize CV risks(Baigent et al. 2011).

The intake of composite hypolipidemic therapies to get lower LDL cholesterol has beneficial effects in minimizing CV events in patients with CKD. PCSK9 (proprotein convertase subtilisin/kexin type 9) is a key regulator of LDL receptors in the liver(Banach et al. 2013, Banerjee et al. 2016). PCSK-9 inhibitors target the PCSK9 protein using monoclonal antibodies or RNA interference(Banerjee et al. 2022). Gene editing with clustered regularly interspaced short palindromic repeats (CRISPR) targeting PCSK9 could be a potential method for reaching the lofty aim of a lifelong "fire and forget" mode to lower LDL-C(Walker et al. 2021). The utilisation of numerous gene editing interventions and other biologics is still under investigation. A maladjusted non-fatal myocardial infarction, non-fatal myocardial infarction, epigenetic response is a component of CV risk, which is exacerbated by chronic renal failure and T2DM. Apabetalone, a specific regulator of the bromodomain and the extraterminal domain transcription pathway, lowers the risk of major CV events in renal patients(Kalantar-Zadeh et al. 2021).

PCSK9 performs pleiotropic effects in the body, including recruitment of the epithelial sodium channel. The 'Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER)' trial looked into the possible advantages of using PCSK9 inhibitors to treat patients with ASCVD and CKD in order to reduce residual risk. It has been demonstrated that using evolocumab is safe and effective in patients with eGFRs above 20 ml/min/1.73 m2, although it is unknown if these effects also apply to people at lesser risk(Charytan et al. 2019). The safety and effectiveness of inclisiran in people with dyslipidemia were demonstrated by data from clinical studies using the drug in the ORION programme (Banerjee et al. 2022). In participants with CKD, renal function did not significantly change, and side effects were comparable in the Inclisiran group and the untreated group.

4. Summary and Recommendations

There are many factors to take in account when choosing the appropriate medication from various treatment options available for T2DM patients. Clinicians must consider HbA_{1c} reduction, mechanisms of action, effect on fasting plasma glucose levels and/or postprandial glucose levels, route of administration, safety and tolerability, impact on weight, and finally cost. Renal dysfunction is a common microvascular complication in T2DM and requires novel therapeutic choices to reduce the burden of renal disease in diabetes. Although the incidence of acute renal failure with the use of GLP-RA is less, but still several cases have been reported in recent studies. Cases of acute kidneyl failure after disease management with DPP-4 inhibitors are rare. Several DPP-4 inhibitors are renally cleared, including saxagliptin, vildagliptin, alogliptin and sitagliptin. Therefore, dose adjustment is required in patients with moderate to severe renal insufficiency. Linagliptin is cleared by the liver and can be used to treat people with all stages of kidney disease without dose adjustment. Similarly, the drugs exenatide (given twice daily and once weekly) and lixisenatide are eliminated renally and are not suggested in patients with severe renal insufficiency. GLP-RA and DPP-4 inhibitors are useful in the treatment of T2DM across the spectrum of HbA_{1c} levels, including patients not taking medication and patients treated with other hypoglycemic therapies. In general, GLP1-RAs are preferred over DPP-4i because greater decline in HbA_{1c} and significant weight loss

have been observed in clinical trials. DPP-4 inhibitors only slightly affect endogenous GLP-1 concentration, resulting in minor glycemic reductions with least impact on weight loss. Given their reduced risk of hypoglycemia, GLP-RA and DPP-4 inhibitors may be preferred in individuals with hypoglycemia unawareness or the elderly. Therefore, individuals with T2DM and CVD, GLP-RAs with proven CV advantage are preferred in the recent guidelines. Thus, the treatment option solely depends upon the patient's specific condition (Table 1).

Additionally, the availability of semaglutide (oral) may be a better option for a patient wishing to avoid injectables. Despite the improvements in the handling of renal risk factors such as hyperglycemia and hypertension, SGLT2 inhibitors are clinically proven nephroprotective drugs with important impacts on risk factors for DN. They are responsible for improving glycemic control and lowering both systolic and diastolic BP. SGLT2 inhibition is also related with weight loss and a decline in uric acid. Both high uric acid levels and obesity are risk factors for DN and for the progression of CKD. Preclinical and clinical studies have exhibited that SGLT2 inhibitor have potentially beneficial renal hemodynamic effects with a decline in hyperfiltration and intraglomerular pressure. A positive influence on albuminuria was continuously documented in clinical studies. However, it must be assumed that these potentially renoprotective drugs are less effective in improving blood glucose control in patients with kidney impairment, so they are used as an add-on therapy to metformin. However, the renal effects on the reductions in body weight and uric acid levels achieved by SGLT2 inhibitors are unknown.

5. Conclusions

The prevalence and incidence of DN are expected to increase if BP, blood glucose, and blood lipids are not adequately monitored to delay the progression of DKD. If left untreated, DKD can eventually lead to ESRD or kidney failure. To develop more effective therapies, in-depth studies on DN's mechanisms and potential drug treatments are essential.

Recently, significant progress has been made in DN research, particularly with the development of hypoglycemic drugs such as SGLT2 inhibitors, GLP-1 inhibitors, and DPP-4 inhibitors, which have shown promising results in clinical studies. Some of these drugs may also benefit patients with proteinuric kidney disease due to other pathological processes.

Clinicians are eager to implement these new therapies in patients with DN for various indications, including reducing cardiovascular risk, even before renal endpoint studies are completed. Many of these drugs are currently in different stages of development, and large-scale randomized controlled trials are being conducted to improve the prognosis of patients with DKD as quickly as possible.

However, the pathogenesis of DKD remains obscure, and drugs targeting specific signalling pathways are still limited. Some drugs have shown effectiveness in animal studies but either not yet tested in clinical trials or lack sufficient clinical trials to confirm their efficacy. Furthermore, some drugs with a preferred beneficial effect on DN may have unsatisfactory safety profiles. Considering these challenges, the journey towards optimal DKD therapy is still ongoing, and continued research and development are crucial to better understand the disease's mechanisms and devise effective and safe treatments.

Conflict of Interest

The authors declare that they have no competing interests.

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Data Availability
All the raw data related to this study is available with the authors.

Authors Contributions
BR and FS conceptualized and organized the study, FB, AI, and QTA did the literature search and analysis, BR wrote the initial manuscript, FS wrote the final manuscript and supervised the project.

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