European Review for Medical and Pharmacological Sciences 2023; 27: 12058-12069

Pharmacotherapeutic considerations and treatment patterns of antihyperglycemic agents for diabetic nephropathy: a review of the literature

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Abstract. – Diabetes can have several macrovascular and microvascular complications in addition to diabetic nephropathy, also referred to as diabetic kidney disease (DKD). DKD is found to occur in approximately 40% of patients with type 2 diabetes and 30% of patients with type 1 diabetes. However, research on the effects of antihyperglycemic agents on the renal outcomes of these patients is still in its infancy. The current review explores glycemic management in patients with DKD, focusing on the challenges faced as well as the clinical considerations of antihyperglycemic agents in this population. A comprehensive literature review was conducted using EMBASE, Web of Science, and PubMed databases. This review was completed by the end of March 2023, and the following keywords were used for the search: diabetic nephropathy, diabetic kidney disease, safety, efficacy, and antihyperglycemic therapies. The several concerns about the use of antihyperglycemic agents in treating diabetes in patients with DKD highlight the need for substantial efforts in educating both patients and healthcare practitioners in this regard. In addition, it is suggested that patients receive individualized treatments, considering the potential long-term benefits of each agent; this would entail prospectively modifying doses in line with the stage of DKD to prevent the progression of renal damage. As some classes of agents offer better renoprotective effects for patients with DKD, it would be wise for nephrologists and endocrinologists to collaborate to offer an antihyperglycemic regime for patients with DKD who are at a high risk of further progression. Further study is needed on the beneficial renal effects of specific classes of agents; more knowledge of their mechanisms and renoprotective effects may contribute to the development of novel treatments for patients with DKD.

Key Words:
Diabetic nephropathy, Diabetic kidney disease, Safety, Efficacy, Antihyperglycemic therapies.

Introduction

Over the past few decades, diabetes has become a major health concern with epidemic proportions, posing a significant threat to personal and societal health. As of 2021, 537 million individuals worldwide, representing 1 in 10 adults, are thought to have diabetes, with low- and middle-income nations being among the hardest hit[1]. The International Diabetes Federation predicts that by 2045, this number will increase to 783 million[1].

Diabetes can have several macrovascular and microvascular complications in addition to diabetic nephropathy, also referred to as diabetic kidney disease (DKD). DKD is found to occur in around 40% of patients with type 2 diabetes and 30% of patients with type 1 diabetes[2]. As the primary cause of renal failure globally[3,4], DKD is indicated by two distinct occurrences separated by at least 3 months of albuminuria (a urinary albumin-to-creatinine ratio above 30 mg/g), a persistent decline in the estimated glomerular filtration rate (eGFR) under 60 mL/min/1.73 m^2, and/or a kidney biopsy evidencing DKD[5]. Over the last two decades, DKD has increased worldwide, especially in certain areas such as the United States, China, India, and Southeast Asia[4]. Consequently, the rate of renal failure due to diabetes is likely to increase twofold by 2030[3].

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DKD is thought to be the primary driver of the excess risk of all-cause and cardiovascular death in patients with diabetes. The 10-year mortality rate has been reported to be 11.5% in diabetic patients without DKD and 31% in patients with both diabetes and DKD[6]. Patients who are diagnosed with DKD have a significantly higher risk of adverse health outcomes, such as cardiovascular disease and death[7-9]. This risk rises substantially in patients with diabetes who are receiving maintenance dialysis for kidney failure. For individuals aged 25 to 34 years in this population, the annual mortality risk rises from 500 to 1,000 times, reaching a rate similar to that of the general population aged 80 years[10].

A prevalent factor for end-stage renal disease, DKD is also a strong independent contributor to cardiovascular morbidity and mortality[11,12]. Nevertheless, early-stage DKD diagnosis and management is generally inefficient or missing. This highlights a 94% increase in DKD-related mortality rate from 1990 to 2012, indicating insufficient efforts in preventing DKD development and progression[13].

Because it has been established that intensive glycemic management can postpone the onset and progression of albuminuria and reduce the decline of GFR in patients with diabetes, attention when selecting the dose and adjusting the antihyperglycemic medication is important to achieve a balance between patient safety and glycemic control. In addition, improving glycemic control is challenging in patients with diabetes due to the increased hypoglycemia risk as well as the changes in the extent to which the kidneys affect glucose homeostasis and in the pharmacokinetics of antihyperglycemic agents[14].

Research[15] on novel antihyperglycemic agents in the dipeptidyl peptidase-4 inhibitor, glucagon-like peptide-1 receptor agonist, and sodium-glucose cotransporter 2 inhibitor classes increasingly highlights the safety and effectiveness of these drugs from both cardiovascular and renal perspectives. Several studies[16] have found that using renin-angiotensin system-blocking agents to meet blood pressure targets in patients with DKD offers better renoprotection than using other agents. However, research on the effects of antihyperglycemic agents on the renal outcomes of these patients is still in its infancy. The current review thus seeks to explore glycemic management in patients with DKD, focusing on the challenges faced as well as the usage considerations of antihyperglycemic agents in this population.

Diabetes Management in Diabetic Kidney Disease (DKD)

Significant progress has been made over the decades in understanding the pathogenesis of proteinuria in DKD, diagnosis, disease screening, prognosis of DKD, and new agents for hypoglycemia. Previous studies[17,18] have shown functional and morphological changes in the renal tubules that are largely involved in the occurrence of DKD and its development. New tubular biomarkers have shown some clinical significance. Several challenges exist in moving to personalized diagnosis and individualized therapies in clinical practice. Clinical studies have highlighted the importance of hyperfiltration and increased reabsorption by sodium-glucose cotransporter-2 (SGLT2) to improve outcomes in DM patients; this has further promoted renal tubule research[18].

Kidneys and Glucose Homeostasis

Through glucose utilization, glucose resorption *via* SGLT, glucogenesis, and glucose transporters, the kidneys play an important role in regulating glucose homeostasis. In patients with T2DM, the renal threshold for glucose excretion is increased, probably due to enhanced regulation of SLGT1 and SLGT2 expression. Increased renal glucose resorption is thought to contribute to the maintenance of hyperglycemia in T2DM patients[19]. The threshold for renal glucose excretion is reduced by elective SGLT2 inhibitors by increasing glucosuria. SLGT2 inhibitors have shown favorable safety and efficacy in T2DM patients in whom hyperglycemia cannot be controlled by exercise, diet, or other glucose-lowering treatments. However, the disadvantages of SLGT2 inhibitors are that they increase the incidence of mild to moderate genital mycotic infections and urinary tract infections; the incidence of side effects associated with decreased volume is increased in elderly patients and patients with GFR less than 60 mL/min/1.73 m^2, and increased LDL cholesterol[20].

Hypoglycemia risk

Chronic kidney disease (CKD) is an independent risk factor for hypoglycemia in diabetes. Furthermore, CKD limits antidiabetic therapies and increases the risk of cardiovascular disease and death. With an increased understanding of pharmacokinetic changes in CKD, the protocol for prescribing diabetes therapies to patients with CDK is changing[21]. Recognition of pharmacoki-

netic changes and application of principles that will reduce the risk of hypoglycemia in patients using insulin secretagogues or insulin are required[22].

Recommendations for Nephropathy Screening in Diabetes

The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) (2007) recommends screening for albuminuria for patients with T2DM once a year after diagnosis. The American Diabetes Association (ADA) recommends urine albumin screening and GFR assessment in T1DM patients at least once every five years (2007). Recommendations for CDK screening issued by the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD) have not changed since 2011. According to the ESC/EASD recommendations, patients with DM and CKD need annual evaluation of urine albumin-creatinine ratio (uACR), GFR, and serum creatinine, along with the recommendations of the patient's physician[23]. Special care should be taken to control blood pressure and glucose; targeting HbA1c (A1c) of less than 7% is recommended to reduce the risk of microvascular complications. Blood pressure should be 130 mmHg in the elderly, while blood pressure in the range of 130 to 139 mmHg is recommended for persons under 65 years of age[23,24].

Glycemic Monitoring in CKD

Glycemic control is essential to delay the complications of DM, which can be a major challenge for physicians. CKD adds another level of complexity to the already high complexity of glycemic control[25]. To control glycemia in CKD patients, it is necessary to know which drugs can be used safely and how kidney disease will affect the metabolism of glycemic drugs used. The glycemic target must be individualized in CKD patients because many parameters may change in the presence of kidney disease[26].

Glycemic goal to attain A1c ~7.0%

The recommended target A1c (ADA recommendations) for DM control is 7% or less, and for certain populations, the ADE recommendations are 8% or less than 6.5%. The American Association of Clinical Endocrinology (AACE) suggests that the A1c target should be less than or equal to 6.5% in healthy individuals with a low risk of hypoglycemia, but also that the targets should be individualized[26,27]. According to KDOQI (2007), recommended A1c in DM and CKD should be lower than 7%, while updated guidelines from 2012 recommend A1c of approximately 7.0%. In T1DM, the development of microalbuminuria is associated with poor glycemic control[26]. Intensive care in T1DM patients leads to a reduction in microalbuminuria. An Epidemiology of Diabetes Interventions and Complications (EDIC) study assessed whether the reduction in the risk of diabetic nephropathy was long-term and found that a reduction in albumin progression and new cases of albumin occurred in the intensive care group rather than the secondary therapy group[26].

Studies[26] involving T2DM patients have shown a reduction in nephropathy progression and in the development of new nephropathy with intensive glycemic control. In T2DM patients, intensive glucose control, with a median A1c in the range of 6.4% to 7.4% at the endpoints related to the kidneys, reduces the risk of developing macroalbuminuria and microalbuminuria[28]. In other studies[26], the difference between A1c in intensive care groups and control groups ranged from 0.6% to 2.3%. The ACCORD study[29] showed a higher risk of mortality and hypoglycemia in T2DM patients treated with intensive glucose-lowering therapy. There was no reduction in the risk of cardiovascular disease in the ACCORD study, and the mean A1c was 6.4%, the same as in the ADVANCE study[30] where the mean A1c was 6.5%[26]. However, up to 21% reduction in nephropathy occurred in the intensive therapy group. The VADT study[31] showed that there is no benefit to the risk of cardiovascular disease when glucose control is strict, and the A1c value is 6.9%. A decrease in A1c leads to benefits for diabetic nephropathy and retinopathy. The effect of A1c is much lower in macrovascular disease. Therefore, an A1c target of approximately 7%, rather than a much lower target, gives an optimal benefit-risk ratio[26].

The glycemic goal in CKD

A lower A1c level can increase the risk of hypoglycemia, and it is necessary to individually adjust the A1c targets. The risks of hypoglycemia, myocardial infarction, cerebral infarction, seizures, or death most commonly occur in the elderly and weak who may have erratic eating habits, CKD, and/or use sulfonylureas and insulin. Multiple A1c targets should be considered for children and patients with a history of severe hypoglycemia, hypoglycemia unconsciousness, or CKD[26,32]. To date, there are insufficient studies and data on ideal targeted blood glucose levels

in patients with CKD stage three or higher. A1c levels greater than 9% and less than 6.5% are associated with increased mortality in the presence of stage 3 CKD or greater, independently of dialysis[33]. Patients with end-stage renal disease benefit from maintaining A1c in the range of 7% to 8% because Ac1 lower than 7% or higher than 8% increases the risk of cardiovascular death and death from all causes. Patients who started dialysis when they were younger than 60 years and who had an A1c greater than 8.5% had poorer survival[26].

Accuracy of A1c

In some patients with kidney disease, hemoglobin A1c may be inaccurate. Factors that contribute to A1c inaccuracies are iron deficiency, hemolysis, and anemia due to the reduced lifespan of red blood cells. Acidosis and carbamylation of hemoglobin may slightly elevate A1c results. Glycated albumin and fructosamine are alternative measures to assess glycemia; each measurement reflects blood sugar concentration over the previous two to three weeks (*vs.* the three-month time frame of A1c). Glycation of albumin is reflected by glycated albumin, while glycation of multiple serum proteins is reflected by fructosamine[34,35]. It is not known whether these measurements provide superior control measures relative to A1c in CKD. There are suggestions that glycated albumin is better than A1c in dialysis patients because A1c tends to underestimate glycemic control in patients with end-stage renal disease. However, other studies[26] claim that A1c is the gold standard.

Anti-Hyperglycemic Medications: Considerations in the Setting of CKD

Many of the drugs used to treat diabetes are metabolized by the kidneys, and impaired renal function can increase the risk of adverse effects. Individualized dose adjustments are necessary.

Because metformin is excreted only *via* the kidneys, it may accumulate in CKD patients. A dose reduction of metformin is recommended in individuals with a GFR of less than 60 mL/min/1.73 m^2. People with CKD have an increased risk of hypoglycemia when sulfonylurea builds up and remains because sulfonylureas are excreted by the kidneys[22,36]. In people with CKD, glipizide, a sulfonylurea, is preferred because it is metabolized in the liver and not the kidneys; other sulfonylureas should be prescribed with caution or avoided. Meglitinides can be used in patients with CKD, but with caution and frequent analysis because they slightly increase the risk of hypoglycemia. DPP-4 inhibitors saxagliptin, vildagliptin, and sitagliptin, may be used in CKD patients, but dose reduction is required due to their accumulation and side effects, while linagliptin does not require dose adjustment because its renal metabolism is minimal[22].

DPP-4 inhibitors can also be used in the last stage of kidney disease. Rosiglitazone and pioglitazone (thiazolidinediones) may be used in CKD and are not associated with an increased risk of hypoglycemia. AKIs are not recommended in people with CKD, but studies[37,38] are not available for most agents, so there is no clear evidence that they increase the risk of hypoglycemia. It is recommended to avoid GLP-1 inhibitors due to the risk of hypoglycemia and also due to lack of evidence. SGLT2 inhibitors, empagliflozin, canagliflozin, and dapagliflozin, do not increase the risk of hypoglycemia but increase the risk of hypovolemia in the elderly with moderate to severe CKD using diuretics. People with any stage of CKD can use insulin, but the dose needs to be adjusted in some cases due to the reduced ability of the kidneys and liver to release glucose[22].

Update on Use of Conventional Anti-hyperglycemic Agents in Diabetes and CKD

Metformin

Warnings regarding the use of metformin in patients with DKD were updated by the FAD in 2016[15,39]. Information on prescribing metformin-containing products has been revised to indicate that metformin can be used safely in patients with mild to moderate renal impairment. In the revision, it was recommended that serum creatinine-based GFR be used to determine renal function and adjust the metformin dose[15,39]. Since metformin was approved (1995) in the US, the recommendations for it in CKD patients have not changed. The revised label noted that metformin should be used with caution in patients with heart failure and during acute liver disease and tissue hypoxia, where there is an increased risk of lactic acid accumulation. A systematic review[15] of metformin use has shown that in CKD patients with congestive heart failure or chronic liver disease, the drug is associated with reduced mortality from all causes. Currently,

limited evidence from clinical data suggests that the overall risk of lactic acidosis in CKD patients using metformin is low[15].

Insulin (rapid-acting insulin, short-acting insulin, intermediate-acting insulin, long-acting insulin)

in patients with CKD, all available insulin preparations can be used, and no reduction in insulin dose is recommended for patients with CKD. To achieve the target glycemic level and limit hypoglycemia, the dose, administration, and type of insulin need to be determined individually[40]. Giving rapid-acting insulin to patients with stage 4 and 5 CKD and dialysis patients is helpful because they often have delayed gastric emptying, so the maximum insulin can be adjusted to the time of postprandial peak blood glucose. Short-acting insulin begins to work 30 to 60 minutes after administration and should be administered 30 minutes before a meal. Medium-acting insulin is dosed twice daily, and its use may be limited by its variable absorption. Long-acting insulin is dosed once a day and has no clear peak, lasting 20 to 24 hours[26,41].

Sulfonylureas

The primary risk with sulfonylureas is hypoglycemia. Glyburide is not recommended in CKD patients because its active metabolites are excreted by the kidneys[15]. Glimepiride can be used in CKD patients, initially in small doses and titrated conservatively. Glipizide is metabolized by the liver, and no dose adjustment is required in CKD patients[15].

Glinides

The main concern with the use of meglitinide in CKD patients is the increased risk of hypoglycemia, so lower drug doses and initial conservative dosing are required[15]. Nateglinide can be used in dialysis patients because hemodialysis removes the active metabolite. In non-dialysis CKD patients with GFR less than 60 mL/min/1.73 m^2, nateglinide should not be used because the active metabolite accumulates. Repaglinide is safe to use in CKD, but it is necessary to start with a minimum dose and slowly titrate upward[26].

Thiazolidinediones

Rosiglitazone and pioglitazone are almost completely metabolized in the liver and no dose adjustment is required. However, the use of thiazolidinedione is avoided in CKD patients because there are concerns about refractory fluid retention, congestive heart failure, higher blood pressure, and an increased risk of fracture[11,15,42].

Other oral medications

The dopamine receptor agonist (bromocriptine) has not been adequately studied in CKD. Bile acid sequestrant (colesevelam) shows no difference in safety and efficacy in patients with GFR less than 50 mL/min/1.73 m^2. However, data for colesevelam are limited because it has not been studied in advanced kidney disease[26,43].

Other Subcutaneous Medications (Glucagon-like peptide 1 (GLP-1) Receptor Agonists, Amylin Analog)

GLP-1 receptor agonists exenatide and liraglutide are Food and Drug Administration (FDA) approved for use with sulfonylureas and metformin and are also used in practice with insulin. With a decrease in GFR, exenatide clearance decreases. There are reports[26] of a patient with CKD and renal impairment where the use of exenatide led to an increase in serum creatinine levels that decreased when drug therapy was discontinued. Cases of acute renal failure associated with the use of exenatide have been reported[26] by the FDA, which does not recommend its use in patients with a GFR of less than 30 mL/min/1.73 m^2 and use with caution when GFR is between 30 and 50 mL/min/1.73 m^2[44]. Liraglutide is metabolized in the kidneys. However, no dose adjustment is indicated, most likely because the data are limited. Dulaglutide and albiglutide do not require dose limits. However, the manufacturer (Eli Lilly and Company, Indianapolis, IN, USA) has reported worsening chronic kidney damage and cases of renal failure, so it is necessary to carefully introduce the drug and increase the dose in patients with nephropathy[45]. The amylin analog (pramlintide) is used as an adjunct to insulin therapy in DM, and no dose adjustment is required in CKD, but this has not been studied in end-stage kidney disease[26].

Considerations for Use of Newer Anti-hyperglycemic Agents in CKD

In 2008, the FDA issued guidelines[15,46] outlining cardiovascular risk assessment expectations for new antihyperglycemic therapies in trials for approval for T2DM treatment. Data from renal and cardiovascular outcomes for new antihyperglycemic agents are available

from targeted cardiovascular outcome studies[15,46] (for DPP-4 inhibitors, SGLT2 inhibitors, and GLP-1 agonists).

Dipeptidyl peptidase-4 inhibitors

Although all available DPP-4 inhibitors can be used in CKD, alogliptin, saxagliptin, and sitagliptin require GFR-based dose titration, while linagliptin does not require dose adjustment based on renal function[47]. In patients with CKD stage three or four, DPP-4 inhibition lowers A1c by approximately 0.5%. All available DPP-4 inhibitors show a potential renal-saving effect as well as a reduction in albuminuria during treatment. As for the effects on albuminuria, it is not known whether they are independent of glycemic changes and changes in blood pressure[15,48].

Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists (GLP-1 RA)

Although the use of GLP-1 RA has been associated with reports of renal impairment, observational studies and clinical studies[15] have not uniformly observed renal impairment. In most cases of a change in kidney function, at least one other factor was involved that contributed to the decrease in kidney function, such as pancreatitis, congestive heart failure, infection, diuretic use, etc.[49]. Studies[15] with DKD patients have shown that liraglutide reduces albuminuria levels and has no adverse effect on GFR in the early stages of CKD and normal renal function. Liraglutide improves glycemic control in T2DM patients with stage three CKD. Dulaglutide and semaglutide reduce albuminuria and the risk of CDK progression. These data suggest that this class of GLP-1 RA has a DKD protection effect. Further research on GLP-1 RA in DKD is pending, and the results should provide answers for the use of new agents such as lixisenatide and dulaglutide[15].

Sodium-glucose co-transporter 2 (SGLT-2) inhibitors

In DKD patients, SLGT-2 inhibitors reduce albuminuria and A1c. Analyses[15] have shown that SLGT-2 inhibitors have beneficial effects on the kidneys, which include slowing the decline in GFR, reducing albuminuria, and reducing the risk of progression to the last stage of kidney disease. Available SGLT-2 inhibitors in the US are empagliflozin, dapagliflozin, and canagliflozin[15]. Results of a study of canagliflozin in DM patients with diabetic nephropathy [Canagliflozin on Renal and Cardiovascular Outcomes in Participants with Diabetic Nephropathy (CREDENCE Trial)] showed that treatment with this agent slows the progression of DKD to the last stage of renal disease and reduces the risk of death from cardiovascular or renal causes[50].

Relationship Between Treatments for Type 2 Diabetes and Long-Term Kidney Outcomes/Effects of Oral Antidiabetic Drugs on Kidney Function

Effective prevention of microvascular complications in DM requires effective glucose control. However, the exact effects of antidiabetic drugs on renal measures such as albuminuria, the incidence of renal disease, and progression to the last stage of renal disease are not fully elucidated[51]. Although more stringent criteria have been used in recent studies[52], only composite endpoints that reveal significant results guided by a surrogate marker are used, not clinical events that are relevant to patients.

Monotherapy Treatments

To prevent chronic complications and improve the quality of life of DM patients, intensive and proper use of drugs and changes in lifestyle (diet, exercise, etc.) are needed from the early stage of T2DM diagnosis[53]. In diabetics who are introduced to their first drug, it is necessary to create a treatment plan according to the clinical characteristics of the patient, the side effects of the drug, its effectiveness, and its price[54]. Metformin is generally recommended as the first treatment for oral hypoglycemic monotherapy because it has an excellent blood glucose-lowering effect, is safe, has few side effects, has a low risk of hypoglycemia, and has little effect on weight gain[55]. However, if it is not possible to use metformin, it is necessary to create another therapy based on the clinical picture of the patient[54].

Metformin monotherapy vs. thiazolidinedione monotherapy

The most common comparative studies[56-58] compare metformin monotherapy with thiazolidinedione monotherapy. Thiazolidinediones are associated with better renal outcomes, i.e., improved GFR and reduced proteinuria, compared to metformin[57]. However, observational studies[58,59] have not found differences between the monotherapies with these two drugs. One study[57] linked thiazolidinediones to a higher risk of renal failure (CKD stage 5, kidney transplantation, and composite dialysis), while this risk was lower with metformin[60,61].

Metformin monotherapy vs. sulfonylurea monotherapy

In studies[58] comparing metformin monotherapy with sulfonylurea monotherapy, metformin was found to be the preferred option. The risk of GFRs falling below 60 mL/min/1.73 m^2 is higher in patients using sulfonylureas than in patients using metformin. Studies[59,61,62] have shown that there is a higher risk of kidney failure (reduced GFR, end-stage renal disease, kidney transplantation, dialysis, and various types of nephropathies) in patients treated with sulfonylureas than with metformin. When proteinuria was used as an outcome, there was no difference between metformin monotherapy and sulfonylurea monotherapy[58]. However, one study reported higher rates of acute dialysis in people who were on metformin monotherapy compared to sulfonylureas monotherapy[60,63].

Sulfonylurea monotherapy vs. thiazolidinedione monotherapy

Lachin et al[57] showed that thiazolidinedione preserves GFR and lowers blood pressure compared to sulfonylureas. Bakris et al[64] associated a decrease in urinary albumin with a thiazolidinedione, while there was no decrease in patients on sulfonylureas. Both studies[57,64] have shown that there is a statistically insignificant difference in the urinary albumin/creatinine ratio[60].

Sulfonylurea monotherapy vs. sodium-glucose cotransporter-2 inhibitor (SGLT2i) monotherapy

Canagliflozin lowers albuminuria, blood pressure, body weight, and A1c, which suggests that it has a protective effect on the kidneys. Canagliflozin leads to a greater decrease in the albumin/creatinine ratio compared to glimepiride[65]. Another study by Wilkinson et al[66] showed that SGLT2i has a greater effect on cardiometabolic risk compared to sulfonylurea**.**

Combination Treatments

In cases where it is not possible to achieve the goal of controlling glycemia with therapy with one antidiabetic drug, it is necessary to immediately start combination therapy involving agents with different mechanisms of action[54,67].

Metformin plus sulfonylurea vs. metformin plus thiazolidinedione

Patients who used the metformin plus sulfonylurea combination had an increased urinary albumin/creatinine ratio compared to the albumin/creatinine ratio with the metformin plus thiazolidinedione combination[60,68].

Sulfonylurea plus metformin vs. sulfonylurea plus thiazolidinedione

Patients who used sulfonylureas plus thiazolidinedione showed decreased urinary albumin/creatinine ratio, while those who used sulfonylureas plus metformin had an increase in the ratio[60,69].

Metformin plus sulfonylurea vs. metformin plus gliptin (DPP4i)

Both combinations of agents reduce albuminuria, with sitagliptin being more likely to reduce albuminuria, independent of glycemic control when combined with metformin[60,70].

Dual vs. Monotherapy

Currie et al[62] showed that patients who used metformin as monotherapy had a lower risk of renal failure compared to patients who used a combination of metformin and sulfonylureas[60]. A study by Hippisley-Cox and Coupland[58] yielded different results, where the risk of renal failure was lower in patients using a combination of sulfonylureas and metformin than in metformin monotherapy[60,61]. There was no difference between the risk of renal failure in patients who received metformin monotherapy and in patients who had a combination of metformin plus thiazolidinedione or metformin plus gliptin. Compared with metformin, patients who used a sulfonylurea plus DPP-4 inhibitor or a sulfonylurea plus thiazolidinedione had a higher risk of renal failure[60,61]. Hung et al[71] have shown that metformin is associated with a lower risk of renal impairment or death compared to sulfonylureas, regardless of changes in A1c, systolic blood pressure, and body mass index.

Strategy for Glycemic Control and Other Risk Factors in Type 2 Diabetes

Most DM therapy guidelines support intensive glycemic control to prevent microvascular and macrovascular complications, although there is no evidence to suggest that strict glycemic control affects the risks of neuropathy, retinopathy, and nephropathy. There is a possibility that the guidelines rely on circumstantial evidence such as surrogate outcomes that are important to patients (microalbuminuria). Reliance on such

outcomes undermines confidence in the value of glycemic control[72]. Evidence supports cautious skepticism about the impact of glycemic control on cardiovascular endpoints and mortality. The use of composite markers that include surrogate outcomes and patient-relevant outcomes may have contributed to the consensus. A significant reduction in the risk of any endpoint associated with DM with strict glycemic control was reported by the UKPDS study[73], although 85% of the effect was limited to retinal photocoagulation only[74,75]. A relative reduction in composite microvascular risk of 14%, where all effects were limited to microalbuminuria and new microalbuminuria, was also reported by the ADVANCE study[30]. The ADVANCE study also reported a 65% reduction in the risk of end-stage renal disease based on several endpoints, which yielded statistically fragile results[76]. ACCORD studies[77] have reported benefits such as delaying the deterioration of visual acuity by three lines, the onset of macroalbuminuria, and loss of ankle sensation. The ACCORD study[78] did not report a significant reduction in microvascular complications. A reduction in the risk of albuminuria progression was also reported by the VADT study, where there was no significant effect on microvascular events[31]. The consensus favoring glycemic control closely reflects evidence for the benefits of strict glycemic control on retinal photocoagulation and surrogate markers of microalbuminuria[75].

Medical Therapy in Dialysis and Post-Transplant Patients in Type 2 Diabetes

Several factors affect and complicate the treatment of DM patients on dialysis. Changes in insulin and carbohydrate metabolism and in the pharmacokinetics of hypoglycemic agents lead to significant glycemic variability. Monitoring glycemic control is challenging, and blood sugar levels are affected by treatment for end-stage kidney failure. Renal impairment affects the physiology of glucose homeostasis because it reduces tissue sensitivity to insulin and insulin clearance.

Glucose control is affected by renal replacement therapy. Peritoneal dialysis can result in hyperglycemia because the dialysate is high in glucose, while hemodialysis can cause hypoglycemia because the dialysate has low glucose concentrations[79]. Asymptomatic hypoglycemia increases the risk of autonomic neuropathy, which is common in DM and CKD. Changes in drug metabolism in CKD limit the pharmacological possibilities to improve glycemic control. Sulfonylureas are not easily removed by dialysis because they are highly bound to proteins such as albumin and may, therefore, accumulate in hemodialysis patients, which may cause hypoglycemia; thus, they should be avoided in hemodialysis patients. Sulfonylureas may be used in the post-transplant period, but glucose levels must be monitored because there is a risk of hypoglycemia when the immunosuppressive dose is reduced[80].

Meglitinides bind to proteins, and therefore, they are unlikely to be eliminated by hemodialysis. Nateglinide is eliminated in the urine and metabolites may accumulate that may lead to prolonged hypoglycemia. Repaglinide is effective for post-transplant diabetes[81]. Metformin should be used in transplant patients when the GFR is greater than 30 mL/min/1.73 m^2 and the body mass index is greater than 25 kg/m^2. Because of the risk of lactic acidosis, metformin should not be used in patients who do not feel well after transplantation. DDP-4 inhibition is recommended in patients on hemodialysis; it does not cause hypoglycemia, but dose adjustment is required for alogliptin, vildagliptin, and sitagliptin. Linagliptin is not removed by hemodialysis and no dose adjustment is required[80].

Data on the use of GLP-1 analogs in hemodialysis and end-stage renal disease are limited, and therefore their use in these patients is not recommended. Limited data on the use of GLP-1 in transplantation suggest that they may be effective in reducing weight and glucose levels without affecting levels of the immunosuppressant tacrolimus[49]. There is conflicting evidence regarding the survival benefits of thiazolidinediones in hemodialysis patients. One[82] study showed rosiglitazone increased mortality from cardiovascular disease and all causes in patients on hemodialysis, while another study[83] showed that patients on thiazolidinediones who do not take insulin had improved survival. Pioglitazone does not require dose adjustment in renal impairment, but its use is not licensed. The use of alpha-glucosidase inhibitors (AGIs) in renal impairment has not been studied and is not recommended in patients with CKD. SGLT2 inhibition is effective and safe in patients with mild to moderate renal impairment but is not recommended in patients on hemodialysis. SGLT2 inhibition leads to a decrease in

A1c and body weight and does not significantly affect GFR, but increases the risk of urinary tract infection[80].

Conclusions

The several concerns about the use of antihyperglycemic agents for treating diabetes in patients with DKD highlight the need for substantial efforts in educating both patients and healthcare practitioners in this regard. Patients should receive individualized treatment, considering their disease states and the potential long-term benefits of each agent; this would entail prospectively modifying doses in line with the stage of DKD to prevent the progression of renal damage. As some classes of agents offer better renoprotective effects for patients with DKD, it would be wise for nephrologists and endocrinologists to collaborate to offer a combination of suitable antihyperglycemic agents for patients with DKD who are at a high risk of further progression. There is also a need for further studies on the beneficial renal effects of specific classes of antihyperglycemic agents; deeper knowledge of their mechanisms and renoprotective effects may contribute to the development of novel treatments for patients with DKD.

Conflict of Interest
The authors declare that they have no conflict of interests.

Funding
The authors declared that no grants were received to support this work.

Availability of Data and Materials
Not applicable.

Authors' Contribution
Ammar Abdulrahman Jairoun review article design and executed article drafting and writing. Chong Chee and Baharudin Ibrahim revised the draft. The final version of the article was approved by all authors for publication.

Ethics Approval
Not applicable.

Informed Consent
Not applicable.

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