

Management of Hyperglycemia in Diabetic Kidney Disease

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The growing incidence and prevalence of diabetes has made a significant impact on the development of diabetic kidney disease (DKD) (1). DKD is among the most frequent complications of diabetes; indeed, diabetes accounts for ~50% of all cases of end-stage renal disease (ESRD) in developed countries (2). Patients often have comorbid diabetes and chronic kidney disease (CKD). Although intensive glyce-mic management has been shown to delay the onset and progression of increased urinary albumin excretion and reduced estimated glomerular filtration rate (eGFR) in diabetes patients (3), conservative dose selection and adjustment of antidiabetic medications is necessary to balance glyce-mic control with safety.

Role of A1C in DKD

A1C has limitations related to its precision and interpretation in the CKD population (4), with erythrocyte turnover being a major cause of A1C imprecision in this population. Red blood cell survival times become shorter as eGFR falls, resulting in a reduction in measured A1C. Treatment with erythrocyte-stimulating agents lowers A1C further, perhaps because of changes in hemoglobin concentrations (5,6).

Observational data support the notion that higher A1C levels in nondialysis diabetes patients with CKD stages 3–5 (eGFR levels <60 mL/min/1.73 m²) are associated with worse outcomes, including progres-

sion of kidney disease (7). However, these patients are at higher risk for hypoglycemic events (8). Factors that may contribute to this increased risk can include slowed elimination of hypoglycemic agents, alcohol intake, chronic malnutrition, acute caloric deprivation, and decreased renal gluconeogenesis as kidney function declines (8–10). In the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study, when compared with patients with normal renal function, those with baseline serum creatinine of 1.3–1.5 mg/dL had a 66% increased risk of severe hypoglycemia (11). A U-shaped relationship between A1C and mortality has been demonstrated, suggesting that hypoglycemia may be one reason for higher mortality in those with A1C levels <6.5% (7,12,13).

Although A1C levels between ~7 and 8% appear to be associated with the highest survival rates in retrospective studies of DKD patients, the previously highlighted limitations of A1C in the setting of DKD makes A1C goal-setting difficult (8). Despite the inherent limitations of A1C measurement, however, A1C remains a key monitoring parameter in the glyce-mic management of people with DKD (12). Importantly, an A1C that is low or trending lower because of a decrease in kidney function may be interpreted as improved glyce-mic control, when it actually may be an ominous sign of kidney disease progression. Ultimately, A1C results should be interpreted carefully

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in conjunction with self-monitoring of blood glucose (SMBG) data.

Use of Drug Therapies for Glycemic Control

As previously noted, the risk of hypoglycemia is increased in people with DKD whose eGFR is <60 mL/min/1.73 m², in part because of decreased clearance of antidiabetic agents and decreased gluconeogenesis by the kidney (9,10). Accordingly, dose adjustments are required for many antidiabetic agents when used in people with DKD. Table 1 provides a summary of dosing recommendations for noninsulin antidiabetic agents currently available in the United States (8,10,14).

Although insulin products are not included in Table 1, insulin clearly requires dose adjustment as kidney function declines, with insulin clearance decreasing in parallel with a decline in eGFR (10,15,16). As is true with insulin use in general, frequent SMBG and appropriate patient-specific dose titration are crucial to achieving individualized treatment goals and avoiding hypoglycemia (10,15,16). Once patients are initiated on chronic dialysis treatment, exogenous insulin requirements often decline further because of reduced insulin resistance and possible malnutrition (17).

Metformin

Per current U.S. labeling, metformin is contraindicated in men with a serum creatinine (SCr) ≥1.5 mg/dL and in women with a SCr ≥1.4 mg/dL (18). Metformin should be used cautiously in patients with heart failure or liver disease and during acute illness or instances of tissue hypoxia, in which the risk of lactic acid accumulation is increased (19,20).

Lactic acidosis can occur in people with diabetes regardless of metformin use, but metformin may be a predisposing factor in the event of serious intercurrent illness (20). Although metformin-associated lactic acidosis (MALA) is a serious concern sup-

TABLE 1. Dosing Recommendations for Noninsulin Antihyperglycemic Agents (8,10,14)

Medication	Recommended Dosing With Impaired GFR (mL/min/1.73 m ²)	Use in Dialysis
<i>Biguanides</i>		
Metformin	<ul style="list-style-type: none"> U.S. prescribing information states: "Do not use if serum creatinine ≥1.5 mg/dL in men, ≥1.4 mg/dL in women" British National Formulary and the Japanese Society of Nephrology recommend cessation if eGFR <30 	Contraindicated
<i>Second-generation sulfonylureas</i>		
Glipizide	<ul style="list-style-type: none"> No dose adjustment required 	No dose adjustment required
Glimepiride	<ul style="list-style-type: none"> Initiate conservatively at 1 mg daily 	Initiate conservatively at 1 mg daily
Glyburide	<ul style="list-style-type: none"> Avoid use 	Avoid use
<i>Meglitinides</i>		
Repaglinide	<ul style="list-style-type: none"> Initiate conservatively at 0.5 mg with meals if eGFR <30 	No clear guidelines exist
Nateglinide	<ul style="list-style-type: none"> Initiate conservatively at 60 mg with meals if eGFR <30 	No clear guidelines exist
<i>TZDs</i>		
Pioglitazone	<ul style="list-style-type: none"> No dose adjustment required 	15–30 mg daily has been used
<i>Alpha-glucosidase inhibitors</i>		
Acarbose	<ul style="list-style-type: none"> Avoid if eGFR <30 	Avoid use
Miglitol	<ul style="list-style-type: none"> Avoid if eGFR <25 	Avoid use
<i>GLP-1 receptor agonists</i>		
Exenatide	<ul style="list-style-type: none"> Not recommended with eGFR <30 	Avoid use
Liraglutide	<ul style="list-style-type: none"> No dose adjustment recommended by manufacturer 	Manufacturer recommends cautious use

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TABLE 1. Dosing Recommendations for Noninsulin Antihyperglycemic Agents (8, 10, 14), continued from p. 215

Medication	Recommended Dosing With Impaired GFR (mL/min/1.73 m ²)	Use in Dialysis
Albiglutide	<ul style="list-style-type: none"> No dose adjustment required for eGFR 15–89, per manufacturer 	No specific dose adjustment recommended by manufacturer
Dulaglutide	<ul style="list-style-type: none"> No dose adjustment recommended by manufacturer 	No dose adjustment recommended by manufacturer
<i>DPP-4 inhibitors</i>		
Sitagliptin	<ul style="list-style-type: none"> 100 mg daily if eGFR >50 50 mg daily if eGFR 30–50 25 mg daily if eGFR <30 	25 mg daily
Saxagliptin	<ul style="list-style-type: none"> 5 mg daily if eGFR >50 2.5 mg daily if eGFR ≤50 	2.5 mg daily
Linagliptin	<ul style="list-style-type: none"> No dose adjustment required 	No dose adjustment required
Alogliptin	<ul style="list-style-type: none"> 25 mg daily if eGFR >60 12.5 mg daily if eGFR 30–60 6.25 mg daily if eGFR <30 	6.25 mg daily
<i>Amylinomimetics</i>		
Pramlintide	<ul style="list-style-type: none"> No dose adjustment required with eGFR >30 Not recommended with eGFR <30 	Avoid use
<i>SGLT2 inhibitors</i>		
Canagliflozin	<ul style="list-style-type: none"> No dose adjustment required if eGFR ≥60 100 mg daily if eGFR 45–59 Avoid use and discontinue in patients with eGFR <45 	Avoid use
Dapagliflozin	<ul style="list-style-type: none"> Avoid use if eGFR <60 	Avoid use
Empagliflozin	<ul style="list-style-type: none"> No dose adjustment required if eGFR ≥45 Avoid use and discontinue in patients with eGFR <45 	Avoid use

ported by published case reports (21), current evidence suggests that the overall risk of MALA is low (20,22). In fact, studies have shown that circulating lactate levels among metformin-treated individuals—even those with impaired kidney function—are typically in the normal range (20).

It has been suggested that eGFR may be a more appropriate measure to assess metformin use when considering that the SCr level can translate into varying eGFR levels depending on a patient's race, age, and muscle mass (10). A recent review proposed that metformin use should be reevaluated at an eGFR <45 mL/min/1.73 m², with a reduction in maximum dose to 1,000 mg/day (20). The review further recommends metformin discontinuation when eGFR falls to <30 mL/min/1.73 m² (Table 2) (20).

Sulfonylureas and Glinides

Hypoglycemia is a primary treatment concern with insulin secretagogue use in general and is of particular importance in the context of DKD (8). Glyburide is extensively metabolized in the liver into several active metabolites that are excreted by the kidney and is not recommended for use in DKD (10,23). Glimepiride is associated with less hypoglycemia when compared to glyburide and should be initiated at a low dose and titrated conservatively, if used (24). Glipizide is metabolized by the liver into several inactive metabolites, and its clearance and elimination half-life are not affected by a reduction in eGFR; thus, specific dose adjustments in patients with DKD are not necessary, and glipizide is generally considered the sulfonylurea of choice in this population (25).

Similar to the sulfonylureas, the main concern with the use of glinides in the setting of DKD is an increased risk of hypoglycemia resulting from decreased renal clearance of the parent drugs and their metabolites (10,26,27). Lower doses of glinides are generally required in people with

TABLE 2. Proposed Considerations for Metformin Use in DKD (20)

eGFR (mL/min/1.73 m ²)	Proposed Action
≥60	<ul style="list-style-type: none"> • No renal contraindication to metformin • Monitor renal function annually
<60 and ≥45	<ul style="list-style-type: none"> • Continue use • Increase monitoring of renal function (every 3–6 months)
<45 and ≥30	<ul style="list-style-type: none"> • Prescribe metformin with caution • Use lower dose (e.g., 50% or half-maximal dose) • Closely monitor renal function (every 3 months) • Do not start new patients on metformin
<30	<ul style="list-style-type: none"> • Stop metformin

DKD; hence, these drugs should be started at conservative doses.

Thiazolidinediones

The thiazolidinediones (TZDs) are nearly completely metabolized by the liver (28–30). Despite the lack of a need for dosage adjustments in patients with DKD, TZD use is generally avoided in this population because of side effects such as refractory fluid retention and increased fracture risk (10,31). Of note for the DKD population, fluid retention secondary to TZD therapy can contribute to the development of heart failure.

Glucagon-Like Peptide-1 Receptor Agonists

Glucagon-like peptide-1 (GLP-1) receptor agonist use has been associated with post-marketing reports of decreased kidney function (32), yet such events have not been noted in clinical trials or population-based observational studies to date (33–35). The majority of case reports of altered kidney function with exenatide have involved at least one contributory factor such as congestive heart failure, pancreatitis, infection, or the use of concomitant medications such as diuretics, renin-angiotensin-aldosterone system inhibitors, and nonsteroidal anti-inflammatory drugs (32). Additionally, patients who experience gastrointestinal adverse events (i.e., nausea, vomiting, or diarrhea) associated with GLP-1 receptor ago-

nist treatment appear to be at greatest risk because these symptoms contribute to a state of dehydration. Table 1 provides current renal dosing recommendations from the manufacturers of currently available GLP-1 receptor agonists.

Dipeptidyl Peptidase-4 Inhibitors

Potential advantages of dipeptidyl peptidase-4 (DPP-4) inhibitor use in DKD are their low risk of hypoglycemia and general weight neutrality (36,37). All of the currently available DPP-4 inhibitors are labeled for use in DKD, but sitagliptin, saxagliptin, and alogliptin require downward dose titration based on eGFR (Table 1) (38). Linagliptin, in contrast, does not require dose adjustment based on renal function (39).

Recent findings from a large cardiovascular outcomes study with saxagliptin indicated a higher risk of hospitalization for heart failure in patients receiving saxagliptin (40). In response to these findings, a meta-analysis of randomized clinical trials of DPP-4 inhibitors was conducted showing the overall risk of acute heart failure to be higher in patients treated with DPP-4 inhibitors than in those treated with placebo or an active comparator (41). Although these findings have raised questions about DPP-4 inhibitors and cardiovascular outcomes, ongoing

studies will provide additional information to clarify this issue.

Sodium–Glucose Cotransporter 2 Inhibitors

Three sodium–glucose cotransporter 2 (SGLT2) inhibitors are currently available in the U.S. (Table 1). SGLT2 inhibitors improve glycemia by increasing disposal of glucose via the urine (42). Because of diminished efficacy as kidney function falls, canagliflozin and empagliflozin are not recommended for use when eGFR is <45 mL/min/1.73 m², and dapagliflozin is not recommended when eGFR is <60 mL/min/1.73 m². SGLT2 inhibitors have been associated with an initial slight decrease in eGFR in clinical trials. This decrease in eGFR may be a hemodynamic effect to decrease glomerular hyperfiltration, with eGFR trending back toward baseline with continued treatment (43).

Recent case reports of euglycemic diabetic ketoacidosis (eDKA) have been reported in patients receiving treatment with SGLT2 inhibitors. It is currently not known whether DKD alters the risk of eDKA in those receiving SGLT2 inhibitor therapy. In a recent U.S. Food and Drug Administration drug safety communication on SGLT2 inhibitor–associated DKA, however, hypovolemia and acute renal impairment were listed as potential factors that may contribute to the development of high anion gap metabolic acidosis (44). Additionally, SGLT2 inhibitors appear to place patients with renal impairment at increased risk of hyperkalemia, particularly when used in combination with potassium-sparing diuretics, ACE inhibitors, and angiotensin II receptor blockers. Health care providers should be cognizant of these potential risks and monitor appropriately.

Longer-term follow-up in large groups of patients with DKD is needed to confirm the safety of SGLT2 therapy in patients with kidney disease (8).

Conclusion

Glycemic management in patients with DKD is complicated by a variety of factors, including, but not limited to, imprecision of A1C measurement and altered pharmacokinetics of antidiabetic agents. Appropriate glycemic goal-setting and use of SMBG are crucial to avoiding hypoglycemia in this population.

Duality of Interest

Dr. Neumiller has received research grant support from AstraZeneca, Janssen, Merck, and Novo Nordisk; has been a consultant to Janssen and Sanofi; and has been a speakers' bureau member for Janssen and Novo Nordisk. Dr. Hirsch has received grant support from Novo Nordisk and Sanofi and has been a consultant to Abbott, Roche, and Valeritas. No other potential conflicts of interest relevant to this article were reported.

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