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Mini review

Choice of Antihyperglycemic Agents in Patients with Chronic Kidney Disease

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Chronic kidney disease (CKD) is one of the most frequent microvascular complications of diabetes. Approximately 40% of adults with type 2 diabetes mellitus (T2DM) have CKD and about 50% of end-stage renal disease (ESRD) is caused by diabetes [1,2]. The hypoglycemia risk is increased in patients with advanced CKD (CKD stages 4 & 5) since clearance of insulin and of some of the non-insulin antihyperglycemic agents is reduced and there is an impaired renal gluconeogenesis with reduced kidney mass [3,4]. The number of non-insulin antihyperglycemic agents that can be used safely to manage diabetes in patients with CKD is therefore, limited and insulin dose usually requires an adjustment to avoid hypoglycemia. It is important that the choice of antihyperglycemic agents is reviewed regularly as CKD stage advances and the doses are readjusted based on CKD stage to avoid hypoglycemia (Table 1).

Table 1: Recommended dose adjustments for antihyperglycemic agents in CKD [1,7,17-19].

Medications		Dose Adjustment Based on CKD Stage	
Class	**Compounds**	**Predialysis CKD (CKD stage 1-4)**	**Dialysis patients (ESRD/CKD stage 5)**
Biguanides	Metformin	No dose adjustment if eGFR>45	Avoid
		Do not initiate if eGFR 30-45	
		Discontinue if eGFR<30	
Sulfonylureas (2nd generation)	Glyburide	Avoid	Avoid
	Glipizide	Initiate conservatively at 2.5 mg daily. No dose adjustment required	Initiate conservatively at 2.5 mg daily. No dose adjustment required
	Glimepiride	Initiate conservatively at 1 mg daily. Dose titration and maintenance dosing should be conservative to avoid hypoglycemia.	Avoid
Meglitinides (glinides)	Repaglinide	Initiate conservatively at 0.5 mg with meals if eGFR<30	No specific dosage adjustments provided in the manufacturer's labeling
	Nateglinide	Initiate conservatively at 60 mg with meals if eGFR<30	No specific dosage adjustments provided in the manufacturer's labeling
Thiazolidinediones	Pioglitazone	No dose adjustment required	No dose adjustment required
α-glucosidase inhibitors	Acarbose	Avoid if eGFR<30	Avoid

	Miglitol	Avoid if eGFR<25	Avoid
DPP-4 inhibitors	Sitagliptin	100 mg daily if eGFR>50	25 mg daily
		50 mg daily if eGFR 30-50	
		25 mg daily if eGFR<30	
	Saxagliptin	5 mg daily if eGFR>50	2.5 mg daily
		2.5 mg daily if eGFR≤50	
	Linagliptin	No dose adjustment required	No dose adjustment required
	Alogliptin	25 mg daily if eGFR>60	6.25 mg daily
		12.5 mg daily if eGFR 30-60	
		6.25 mg daily if eGFR<30	
Bile acid sequestrants	Colesevelam	No dose adjustment required	No dose adjustment required
Dopamine-2 agonists	Bromocriptine (quick release)	No dosage adjustments provided in the manufacturer's labeling	No specific dosage adjustments provided in the manufacturer's labeling
SGLT2 inhibitors	Canagliflozin	No dose adjustment required if eGFR>60	Avoid
		100 mg daily if eGFR 45-59	
		Avoid if eGFR<45	
	Dapagliflozin	Avoid if eGFR<60	Avoid
	Empagliflozin	No dose adjustment required if eGFR ≥45	Avoid
		Avoid if eGFR<45	
	Ertugliflozin	Avoid if eGFR<60	Avoid
GLP-1 receptor agonists	Exenatide	Not recommended with eGFR<30	Avoid
	Exenatide (extendedrelease)	Not recommended with eGFR<30	Avoid
	Liraglutide	No specific dose adjustment recommended by the manufacturer	Limited experience. Manufacturer recommends cautious use.
		No dose adjustment required if eGFR>15	No specific dosage adjustments provided in the manufacturer's labeling
	Albiglutide	No dose adjustment required if eGFR≥30	Avoid
	Lixisenatide	No dosage adjustments provided in the manufacturer's labeling if eGFR 15-29	
	Dulaglutide	No specific dose adjustment recommended by the manufacturer	Limited experience. Manufacturer recommends cautious use.
	Semaglutide	No dose adjustment required per manufacturer	No dose adjustment required per manufacturer
Amylin mimetics	Pramlintide	No dose adjustment required if eGFR>15	Limited experience. No specific dosage adjustments provided in the manufacturer's labeling
Insulins		Lower insulin doses required with a decrease in eGFR.	Lower insulin doses required with a decrease in eGFR.

Metformin is recommended as monotherapy of choice in patients with T2DM, and it is mostly eliminated unchanged in the urine. Lactic acidosis is a rare and serious side effect of metformin in CKD patients. The previous black box warningstated that metformin was contraindicated in men with a serum creatinine >1.5mg/dL and women >1.4. The United States Food and Drug Administration (FDA) revised the warnings in 2016, and the new recommendation indicates that it can be continued until eGFR is 30mL/min/1.73m^2 and that it can be initiated if it is >45mL/min/1.73m^2 [5].

First-generation sulfonylureas (chlorpropamide, tolazamide, and tolbutamide) are contraindicated in CKD due to increased half-lives and the risk of hypoglycemia. Of second-generation sulfonylureas, glyburideis not recommended for use in CKD as its active metabolites are eliminated in urine. Glimepiride is primarily metabolized by the liver, but its active metabolites are excreted by kidney;it can be used with the dose reduction in CKD. Glipizide ismetabolized by the liver and mainlyeliminated in the urine as inactive metabolites. Therefore,dose adjustmentisusually not

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required and it is considered the preferred choice of sulfonylureain CKD [6,7]. Of glinides, repaglinideis metabolized by the liver and mainly excreted in the feces; therefore, with a lower starting dose, it can be used in advanced CKD or ESRD. However, active metabolites of nateglinideare mostly eliminated in urine, and thus it should be used with caution in advanced CKD [7,8]. The thiazolidinedione, pioglitazone, is metabolized by the liver; therefore, dosage adjustment is not necessary. Acarbose and miglitol, α-glucosidase inhibitors, are not significantly absorbed from the gastrointestinal tract, but increased levels of the metabolites are observed in CKD. Therefore, these agents are not recommended in patients with eGFR<30mL/min/1.73m^2 [4].

Dipeptidyl peptidase (DPP-4) inhibitors are usually effective and relatively safe in CKD and ESRD patients.Saxagliptin, alogliptinand sitagliptinrequire dose adjustmentin CKD. Dose reduction is not needed for linagliptin since renal excretion is low [9,10]. Of GLP-1 receptor agonists, exenatide is predominantly excreted via the kidney; therefore, it is not recommended in patients with eGFR<30mL/min/1.73m^2 [11]. Other GLP-1 receptor agonists do not require dosage adjustment [12]. The glycemic efficacy of sodium-glucose cotransporter 2 inhibitors depends on glucose filtration through the kidney, and therefore these are not recommended in patients with advanced CKD. Dapagliflozinshould be avoided in patients with eGFR<60mL/min/1.73m^2 since it is primarily excreted by the kidney. Ertugliflozin has minimal urinary excretion, but there is the increased exposure with declining renal function,and thus it is not recommended in those with eGFR<60 mL/min/1.73m^2 [13]. Empagliflozin and canagliflozinareexcreted in both feces and urine and are not recommended if eGFR is <45 [14-16].

For most hemodialysis patients or in advanced CKD, insulin is the effective and probably safer option. There is a higher risk of hypoglycemia due to reduced renal clearance, and therefore a reduction in the starting dose and gradual dose titration is recommended [17]. For hemodialysis patients and for CKD patients with eGFR<10mL/min/1.73m^2, the initial dose of insulin should be decreased by as much as 50 percent [18]. In summary, an impaired renal function may significantly affect the pharmacokinetics of the most antihyperglycemic agents, which may result in a higher risk of side effects, especially hypoglycemia [19]. Therefore,it is important to check renal function regularly and monitor the progression of kidney disease in the patients with diabetes. The choice and dosage of antihyperglycemic agents should be reviewed and re-adjusted as eGFR declines.

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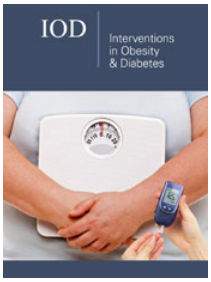

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