

## Review Article

# Management of Hyperglycemia in Patients with Chronic Kidney Disease and Dialysis

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The incidence of diabetes mellitus (DM) is growing rapidly. It is well known that intensive glycemic control prevents or delays progression of the micro and macrovascular complications in patients with DM, but it is not clear in patients with DM and chronic kidney disease (CKD). The guidelines recommend a target HbA1c < 7.0% for prevention of diabetic complications. Management of hyperglycemia is very difficult in these patients and it is recommended that lifestyle modifications (cessation of smoking, weight reduction, increased physical activity and dietary changes) be used in all patients with DM, whether medication is used or not. Sulfonylureas and meglitinides are associated with a risk of hypoglycemia. Metformin should not be used when eGFR (estimated glomerular filtration rate) is <30 ml/min per/1.73 m<sup>2</sup>. Glitazones may cause fluid overload and should be avoided in CKD. Newer DPP-IV inhibitors may be used in CKD, but experience is as yet very limited. Physicians recommend avoiding GLP-1 analogs when eGFR is <60 mL/min/1.73 m<sup>2</sup>. The SGLT-2 inhibitors are only effective with intact kidney function and are contraindicated in dialysis patients. Management of hyperglycemia is very complicated and should be individualized in patients with CKD. In this review, we will discuss non-insulin and insulin-based therapies in patients both CKD and dialysis.

**Keywords:** Hyperglycemia; Chronic kidney disease; Dialysis**Abbreviations**

DM: Diabetes Mellitus; CKD: Chronic Kidney Disease; UKPDS: United Kingdom Prospective Diabetes Study; ADVANCE: Action in Diabetes and Vascular Disease-Preterax and Diamicon Modified Release Controlled Evaluation; DCCT: Diabetes Control and Complications Trial; ACCORD: Action to Control Cardiovascular Risk in Diabetes; VADT: Veterans Affairs Diabetes Trial; K/DOQI: Kidney Disease Outcomes Quality Initiative; eGFR: Estimated Glomerular Filtration Rate; SU: Sulfonylurea's; PPAR- $\gamma$ : Peroxisome Proliferator-Activated Receptor Gamma; GLP-1: Glucagon Like Peptide-1; DPP-IV: Dipeptidyl Peptidase IV; SGLT-2: Sodium-Glucose Cotransporter-2; HD: Hemodialysis; PD: Peritoneal Dialysis; HbA1c: Hemoglobin A1c

**Introduction**

Diabetes Mellitus (DM) is the main cause of chronic kidney disease (CKD). Given the prevalence of DM is estimated to increase from 366 million patients in 2011 to 552 million patients in the year 2030, with increasing prevalence of DM particularly in Asia. The kidney plays role in insulin resistance and gluconeogenesis, when renal failure progressed, insulin clearance is markedly reduced and the patients with CKD sensitive to hypoglycemia. Additionally, reduced drug clearance and a greater risk of hypoglycemia with used medications will further complicate the management of hyperglycemia in patients with CKD. However, the goals and methods concerning glycemic control in these patients are not clearly defined. Because safer and more effective pharmacological therapy is available, an individual approach to DM in the CKD patients is essential [1-3].

The physicians know that there is an association between poor glycemic control and microvascular complications (nephropathy, retinopathy, and neuropathy) in diabetic patients. Intensive glycemic control has favorable effect on nephropathy than conventional therapy in both type 1 and type 2 DM. Results of the studies evaluating the effect of intensive glycemic control on renal complications are miscellaneous. In UKPDS (UK Prospective Diabetes Study), intensive glycemic control was found associated with decrease in HbA1c values (7.0%), microalbuminuria (RR, 0.76; 99% CI), proteinuria (RR, 0.67; 99% CI), a doubling of serum creatinine (RR, 0.40; 99% CI) and a persistent decrease in the risk of microvascular events (24% relative reduction at 10 years) in patients with recently diagnosed type 2 DM [4]. Similarly, the ADVANCE (Action in Diabetes and Vascular Disease-Preterax and Diamicon Modified Release Controlled Evaluation) trial showed that intensive glycemic control is also associated with a significant reduction in renal complications (new or worsening nephropathy, development of macroalbuminuria, new-onset microalbuminuria) [5]. The DCCT (Diabetes Control and Complications Trial) study indicated that intensive glycemic control in patients with type 1 DM was significantly improved both microalbuminuria and macroalbuminuria [6]. In contrast, the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial, a prospective interventional study recruited 10,251 patients with DM without renal failure, and as intensive glycemic control resulted with increase in all cause mortality, was terminated early [7]. Likewise, post-hoc analyses from the ADVANCE trial showed that severe hypoglycemia significantly increased the adjusted risks of macrovascular events [8]. Also, the VADT (Veterans Affairs Diabetes Trial) showed that more intensive glycemic control did not meet the

expectations in decreasing severe kidney complications (doubling of serum creatinine, creatinine >3 mg/dl or GFR <15 ml/min) or on the rate of GFR reduction [9].

When determining treatment of hyperglycemia in patients with CKD, the physicians should consider adverse effects, risk of hypoglycemia, tolerability and patient compliance. Adequate patient education and lifestyle modifications (cessation of smoking, weight reduction, increased physical activity and dietary changes) are first steps in hyperglycemia management. In this review, we discussed therapeutic options (non-insulin and insulin treatment) used in patients with diabetes and CKD in detail to provide a guide to physicians in optimum choice of treatment.

## Non-Insulin Antihyperglycemic Treatment

**Metformin** is a biguanide reduces both hepatic gluconeogenesis and glucose output, hypoglycemia is unlikely. The drug is eliminated via the kidneys mainly by glomerular filtration and tubular secretion [10,11]. Therefore, there is a risk of lactic acidosis because of accumulation of the drug in patients with CKD. It should not be used in men with a serum creatinine (SCr) of  $\geq 1.5$  mg/dl or women with a SCr of  $\geq 1.4$  mg/dl. However, in weak and elderly patients serum creatinine levels may be misleading, so, eGFR should be used. The exact eGFR cutoff for metformin use to avoid lactic acidosis is controversial. The clearance of metformin decreases 75% when the GFR < 60 mL/min/1.73 m<sup>2</sup> without further change when the eGFR declines to 30 mL/min/1.73 m<sup>2</sup>. Even with these levels of eGFR through metformin associated lactic acidosis is extremely rare. Given its marked clinical benefit restriction of metformin use based on the creatinine cutoffs is difficult. The guidelines suggest that metformin may be used in patients with an eGFR >45 ml/min/1.73 m<sup>2</sup> and stopped eGFR <30 ml/min/1.73 m<sup>2</sup>. The use of metformin among patients with eGFR between 30 and 44 ml/min/1.73 m<sup>2</sup> is reassessed by the physician. Metformin has not been trialled in the dialysis setting [12,13].

**Sulfonylureas (SU)** increase insulin secretion by stimulating beta cells and reduce blood glucose. They have been used for the management of type 2 DM for over more than five decades. SU are strongly protein bound, particularly to albumin, and can be displaced from albumin by many drugs which CKD patients take (salicylates, warfarin, and beta-blockers). The first-generation SU (chlorpropamide, acetohexamide, tolbutamide and tolazamide) are almost exclusively excreted by the kidney and can accumulate in CKD patients. These can contribute to the development of hypoglycemia and are contraindicated. Second-generation SU (glipizide, glimepiride, glyburide, gliclazide) are metabolized in the liver and active metabolites are excreted in the urine [14]. They should be used with caution in patients with mild CKD (eGFR 60-90 ml/min/1.73 m<sup>2</sup>) and are contraindicated in eGFR <60 ml/dk/1.73 m<sup>2</sup>. However, glipizide and gliclazide particularly glipizide, as it does not have active metabolites, are recommended for CKD patients with eGFR 45-60 ml/min/1.73 m<sup>2</sup> and no dose adjustment is necessary in dialysis patients. They are metabolized in the liver and excreted in the urine as inactive or weakly active metabolites. The suggested dose of glipizide is 2.5 to 10 mg/day and gliclazide is 80-320 mg/day [12].

**Meglitinides** are very short acting insulin secretagogues

that stimulate pancreatic beta cells. Nateglinidine is hepatically metabolized, with renal excretion of active metabolites and so nateglinide should be used with caution when the eGFR is <30 mL/min/1.73 m<sup>2</sup>, starting with 60 mg at meals and cautiously titrating upwards [15]. On the other hand, repaglinide is almost completely transformed to inactive metabolites in the liver and only 10% is excreted by the kidneys. Although hypoglycemia has not been demonstrated to increase substantially with progressive falls in eGFR, it would seem rational to start treatment cautiously with a 0.5 mg of repaglinide with each meal and titrate upwards cautiously when the eGFR is <30 mL/min/1.73 m<sup>2</sup>. Because of risk of hypoglycemia, meglitinides are not recommended for patients on dialysis [16,17].

**Glitazones/Thiazolidinediones** improves insulin sensitivity by acting on the peroxisome proliferator-activated receptor gamma (PPAR-  $\gamma$ ) receptors, mainly in skeletal muscle and adipose tissue. Both pioglitazone and rosiglitazone are not associated with hypoglycemia as they do not accumulate in CKD [18,19]. However, they may lead to fluid retention so must be avoided in patients with CKD and dialysis when over-volemia is issue such as severe nephrotic syndrome or cardiac failure. They are also associated with increased fracture rate and must be used cautiously in patients with renal osteodystrophy [20-22].

**Alpha-Glucosidase Inhibitors** inhibit the intestinal alpha-glucosidase enzyme; therefore reduce absorption of glucose from the intestine. In CKD, drug levels and active metabolites are increased and may cause liver failure. Both acarbose and miglitol are not recommended in patients with CKD, especially eGFR is < 25-30 mL/min/1.73 m<sup>2</sup> and patients on dialysis [12,14,23].

**Glucagon like peptide-1 (GLP-1) analogues** (exenatide and liraglutide) are injectable incretin mimetics that facilitate insulin secretion, decrease glucagon secretion, delay gastric emptying and cause early satiety. These drugs show diuretic effect via GLP-1 receptors expressed in renal tubules and may aggravate renal impairment, especially in patients treated with renin-angiotensin system inhibitors or diuretics. Exenatide is excreted by the kidneys, and its clearance is reduced by 36% with a eGFR of 45 mL/min/1.73 m<sup>2</sup> and by 64% with a eGFR of <30 mL/min/1.73 m<sup>2</sup>. Therefore, exenatide is not recommended for use with a eGFR < 30 mL/min/1.73 m<sup>2</sup> [24,25]. Liraglutide is fully degraded elsewhere other than kidney in the body. In single dosing, there is no effect on the area under the curve in subjects with stages 4 and 5 CKD. However, the experience with liraglutide is very limited in patients with CKD. Physicians recommend avoiding this medicine when eGFR is <60 mL/min/1.73 m<sup>2</sup> [12,26].

**DPP-IV Inhibitors (Gliptins)** improve both fasting and post-prandial glucose levels by inhibiting the dipeptidyl peptidase IV (DPP-IV) enzyme. All gliptins are mainly excreted by kidney and there is a little trial data for their use. Sitagliptin is eliminated predominantly unchanged, via the urine (87%) or via the feces (%13). Therefore, the half-life of sitagliptin is increased in patients with renal failure. The suggested dose of sitagliptin is 50 mg/day if eGFR is 30-50 mL/min/1.73 m<sup>2</sup> and 25 mg/day if eGFR is <30 mL/min/1.73 m<sup>2</sup> or on dialysis, irrespective of dialysis timing [27]. Vildagliptin also is eliminated approximately 85% in the urine, because of this, it is contraindicated in patients with eGFR <50 mL/min/1.73 m<sup>2</sup>.

**Table 1:** Non-insulin and insulin preparations in CKD and dialysis patients.

CLASS	DRUG	RELIABLE USE IN CKD	USE IN DIALYSIS
Biguanide	Metformin	sCre $\leq$ 1.5 mg/dl in men sCre $\leq$ 1.4 mg/dl in women	NO
Sulfonylureas	Glipizide	eGFR $>$ 45 ml/min/1.73m $^2$	NO
	Gliclazide	eGFR $>$ 45 ml/min/1.73m $^2$	NO
	Glimepride	eGFR $>$ 60 ml/min/1.73m $^2$	NO
Meglitinides	Repaglinide	eGFR $>$ 30 ml/min/1.73m $^2$	YES
	Nateglinide	eGFR $>$ 30ml/min/1.73m $^2$	NO
Glitazone	Pioglitazone	eGFR $>$ 60 ml/min/1.73m $^2$	NO
Alpha-glucosidase inhibitors	Acarbose	eGFR $>$ 60ml/min/1.73m $^2$	NO
GLP-1 analogs	Exenatide	eGFR $>$ 30ml/min/1.73m $^2$	NO
	Linagliptide	eGFR $>$ 60 ml/min/1.73m $^2$	NO
DPP-4 inhibitors	Sitagliptin	eGFR $>$ 30ml/min/1.73m $^2$ with dose adjustment	NO*
	Vildagliptin	eGFR $>$ 50ml/min/1.73m $^2$ *	NO
	Saxagliptin	eGFR $\geq$ 50ml/min/1.73m $^2$ with dose adjustment	NO*
	Linagliptin	No dose adjustment*	NO
Rapid acting insulin	Regular, Lispro, Aspart	Reduce dose by 25% when e GFR is 10-50 ml/dk	Reduce dose by 50%
Long acting insulin	Neutral protamine, Glargine, Detemir	Reduce dose by 25% when e GFR is 10-50 ml/dk	Reduce dose by 50%
Premixed insulin	70/30 human mix, 70/30 aspart mix, 75/25 lispro mix	Reduce dose by 25% when e GFR is 10-50 ml/dk	Reduce dose by 50%

\*Limited experience, with caution

However, a recent 24 week study suggested that vildagliptin is effective and safety in patients with moderate-severe renal impairment [28]. Saxagliptin is eliminated both by biotransformation and by renal excretion. The use of saxagliptin is not recommended for patients with severe renal failure. On the other hand a randomised controlled study (52 week) suggested that it is effective and well tolerated [29]. K/DOQI guidelines recommended that if eGFR is  $\leq$  50 mL/min/1.73 m $^2$  saxagliptin can be used 2.5 mg/day. A 4-hour hemodialysis (HD) session removed 23% of the saxagliptin dose and therefore it should be taken 2.5 mg daily after dialysis [12,30]. Linagliptin is eliminated is highly low (1%) in the urine and no dose adjustment is required for any degree of renal failure [31].

Additionally, both DPP-IV inhibitors and GLP-1 receptor agonist may exert a renoprotective effect by reducing inflammation and fibrosis and blood pressure and improving cardiac and vascular function [32,33].

**Sodium-Glucose Cotransporter-2 (SGLT-2) Inhibitors** (canagliflozin, dapagliflozin, empagliflozin) are novel hypoglycemic agents. Their mechanism of action is insulin-independent, they block the reabsorption of glucose and sodium via the SGLT-2 transporter in the proximal tubule, which decreases the capacity for renal glucose reabsorption and reduces the renal threshold at which glucose is excreted resulting in net loss of excess glucose in the urine, consequently reduce blood glucose. Also, they may exert a renoprotective effect by lowering glomerular hyperfiltration, limiting hyperglycemia-induced damage to proximal tubule, reducing blood pressure and causing weight loss. The SGLT-2 inhibitors are only effective with intact kidney function and are not recommended in dialysis patients [34-36].

**Amylin** is an important neuroendocrine hormone which is secreted by pancreatic beta cells with insulin in response to a meal.

Thus, slowing of gastric emptying and inhibiting glucagon release, it plays a significant role in glucose homeostasis, particularly postprandially. Pramlintide is an amylin analog and metabolized by the kidneys. This agent is used an adjunct injectable therapy in patients who require prandial insuline coverage with type 1 and type 2 DM. Pramlintide has not been studied in patients with CKD [37,38].

Recommendations about the use of non-insulin and insulin preparations in CKD and dialysis patients are summarized in Table 1.

## Insulin Treatment

Insulin is used in the treatment of all types of DM. The liver is the main site of insulin clearance, removing approximately 75% during the first portal passage and the remainder clearance is via the kidney. With a molecular weight of 6000 Da, insulin is freely filtered. Of the total renal insulin clearance, approximately 60% occurs by glomerular filtration and 40% by extraction from the peritubular vessels. Less than 1% of filtered insulin appears in the urine. In patients with DM receiving exogenous insulin, renal metabolism plays a key role since there is no first pass metabolism in the liver. As renal failure progresses, insulin clearance decreases and this situation is compensated with an increment in insulin uptake by proximal tubule. If eGFR  $<$ 60 mL/min/1.73 m $^2$ , insulin clearance is markedly reduced. At the same time, insulin catabolism in liver and muscle decreases during uraemia and insulin half-life time increases. Both decreased clearance of insulin and impaired renal gluconeogenesis with reduced kidney mass leads to hypoglycemia and weight gain in CKD patients [39], therefore it should be used with caution in these patients.

Several different insulin preparations such as rapid acting insulin (regular, lispro, aspart, glulisine), long acting insulin (Neutral protamine Hagedorn, Glargine, Detemir) and premixed insulin (70/30 human mix, 70/30 aspart mix, 70/25 lispro mix) can be used

**Table 2:** Monitoring glycemic control in patients with DM and CKD.

	HbA1c (%)	Fasting Blood Glucose (mg/dl)	Postprandial Blood Glucose (2. Hour-mg/dl)
eGFR>60ml/min/1.73m <sup>2</sup>	<6.5	80-120	<140
15<eGFR<59ml/min/1.73m <sup>2</sup>	<7.5	100-120	<140-160
Dialysis patients			
age<50 years	<7-7.5	100-140	<200
age>50 years	<7.5-8		

to regulate blood glucose. There is no a consensus about the choice of insulin in patients with CKD. Both a short onset of action and a short duration of action rapid acting insulin analogs can be eligible. Because of decrease the risk of late hypoglycemic episodes the therapy may be rearranged with insulin glargine or NPH insulin can be used for basal requirements, along with lispro or aspart before meals two or three times daily. The principles of insulin therapy for CKD patients are not different from general diabetic patients. In patients with Type I DM insulin therapy should be started at 0.5-1 IU/kg and Type II DM should be started 0.3-0.5 IU/kg with no dose adjustment is if the GFR is > 50 mL/min/1.73 m<sup>2</sup>. When GFR is 10-50 mL/min/1.73 m<sup>2</sup>, the total insulin dose should be reduced by 25% and by 50% if GFR <10 mL/min/1.73 m<sup>2</sup> [12,40,41]. The dose should be titrated upward, as indicated by blood glucose monitoring and most patients will require more insulin than this initial dose.

Both improvements in insulin resistance associated to dialytic procedure and decrease in insulin clearance because of loss of renal function reduce insulin requirement in diabetic HD patients. Suzuki et al. reported that 1 year after HD starting 30% of diabetic patients did not need insulin, whereas less than 20% of diabetics treated with oral agents were insulin dependent [42]. Although intensive glycemic control in dialysis patients have been reported to be beneficial in a few small studies [43,44], larger observational studies have found no significant correlation between tight glycemic control and survival [45,46]. In a meta-analysis (10 studies and 83.684 participants) there was an increased mortality associated with both high levels HbA1c ≥ 8.5% (6 studies; HR, 1.29; 95% CI, 1.23-1.35) and low levels HbA1c levels ≤ 5.4% (6 studies; HR, 1.09; 95% CI, 0.89-1.34) [47].

Continuously explosion to high concentrations of glucose in peritoneal dialysate makes difficult to achieve good glycemic control in diabetic peritoneal dialysis (PD) patients. Both intraperitoneally and subcutaneously insulin is acceptable therapy for these patients. Intraperitoneally insulin therapy may have some advantages such as direct delivery of insulin to the liver, more physiologic absorption, avoids injections, better insulin sensitivity, prevention of insulin antibody formation and major fluctuations in blood sugar. On the other hand, a higher cost, need for higher dose of insulin, increased peritonitis risk, induction of subcapsular steatosis, malignant omentum syndrome are the disadvantages [48-50]. Daily use of solutions with low concentrations of glucose, icodextrin and amino acids may be useful in improving glycemic control in PD patients. On account for this, the choice of insulin therapy depends on physician and patient preference.

## Assessment and Monitoring Glycemic Control

The glycemic control in patients with DM and CKD as do in patients with DM and normal kidney patients. Fasting blood glucose, postprandial blood glucose (2 hours) and hemoglobin A1c (HbA1c)

measurements are standard to assess chronic glycemic control in diabetic patients with CKD. Its explication is further complicated by a reduced red cell lifespan, iron deficiency, repeated blood transfusions and erythropoietin use. Both glycated albumin and fructosamine have been proposed as alternative biomarkers of glycemic control, but there is no consensus. All drugs (except acarbose) decrease HbA1c levels approximately 1-1.5%. The guidelines suggest that non-dialysis patients who are risk for hypoglycemia should not be treated to HbA1c <7%, and that the target HbA1c should be over 7% in patients who have comorbidities or limited life expectancy. Additionally, among dialysis patients who are relatively young (<50 years) and without significant comorbid conditions, the HbA1c target is closer to 7-7.5%. However, among older patients with multiple comorbid conditions, the HbA1c target is closer to 7.5-8% [12,51,52]. Recommended glycemic control parameters for diabetic patients with renal disease are listed in Table 2.

## Conclusion

CKD is associated with insulin resistance and, in advanced CKD, decreased insulin degradation. Glycemic control in these patients can be difficult, because of DM, renal insufficiency, pharmacological and dialysis therapy. It is well known that good glycemic control in the predialysis patients is essential in improving long term prognosis in diabetic patients on dialysis. Good glycemic control before dialysis was closely correlated with morbidity and mortality in both HD and PD patients. But it is not clear what the benefit of intensive blood glucose control is on progression in patients who have reached ESRD. Careful, individualized therapy is essential among patients with advanced CKD or on dialysis.

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