Insulin Therapy in Diabetic Nephropathy

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Agenda

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- Glucose homeostasis in CKD.
- Insulin requirements in patients with diabetes and progressive renal disease .
- Glycemic target in CKD.
- Insulin regimen options in patients with diabetes on maintenance hemodialysis (MHDx).
- Management of hyperglycaemia in hospital dialysis unit.
- Summary

Introduction

- In individuals with in either type 1 or type 2 diabetes, it has been reported that ***25 – 40%*** will develop diabetic nephropathy in a 25 –year period.
- Diabetes is considered to be the **leading cause** for ESRD: The proportion of diabetes -related ESRD among all cases of ESRD is reported to be about ***25 –55%.***
- More than ***50%*** of patients with DKD stages 4 and 5 have been reported to be on insulin therapy.

Glucose homeostasis in CKD

- **uremic environment:**
- Reduces hepatic degradation of insulin and leads to accumulation of insulin.
- Insulin secretion can also be impaired in uremia.
- Metabolic acidosis may lead to suppression of insulin release, and elevated parathyroid hormone may also lead to increased intracellular calcium, which blunts the release of insulin from pancreatic -cells.
- Deficiency of active vitamin D may also be important in insulin secretion; administration of active vitamin D enhances insulin release.
- A true decline in blood glucose concentration in patients with progressive nephropathy may be a result of malnutrition.

- CKD is an **insulin resistant** state. A number of mechanisms for this have been suggested, including the presence of **uremic toxins**, excess **parathyroid hormone** due to deficiency of active vitamin D (1,25 dihydroxyvitamin D), or **anemia** leading to reduced skeletal muscle glucose uptake and diminished glycogen synthesis.

- Some of these hypotheses are evidenced by the fact **that dialysis can significantly improve insulin sensitivity by removal of "uremic toxins",** administration of active vitamin D may enhance insulin sensitivity, and improved glucose uptake is seen following correction of anemia with erythropoietin.

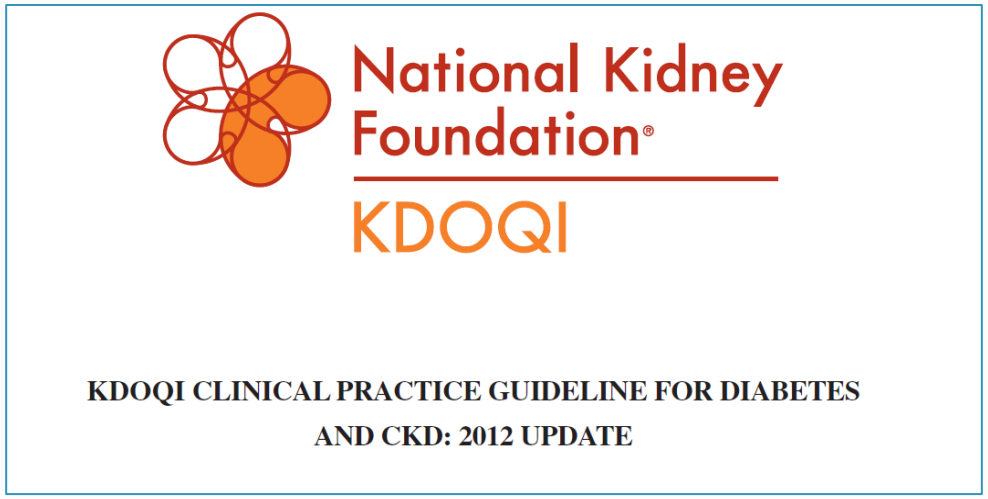
- The reduction in insulin clearance rate only becomes clinically significant at significant levels of renal impairment (***eGFR <20 mL/ min***), as increased tubular uptake is able to compensate. Once GFR is sufficiently low, however, insulin degradation may become markedly reduced, leading to a significant **risk of hypoglycaemia**.

Insulin metabolism in patients with end stage renal failure

- In non-diabetes individual, ***40–50%*** of insulin secreted by the pancreas is extracted through liver during its first passage. The remainder is degraded, to a lesser extent, in kidney, muscle and most other tissues.

- Exogenous insulin is primarily metabolized by kidney (***30–80%***), unlike by liver in non-diabetes individuals.

- *In CKD, insulin action can change individually in an* ***unpredictable manner:***
- Peripheral insulin **resistance** increases while **renal gluconeogenesis** and hypoglycemic **counter –regulation** decreases. The **clearance of insulin and other anti-hyperglycemic** agents declines, which results in pharmacokinetic and pharmacodynamics changes with increased risk of hypoglycemia.



Glycemic target in CKD

- The KDOQI 2012 guideline for diabetes and CKD recommends a target HbA1c of **~7.0%.**
- The target HbA1c is recommended be **>7.0%** in individuals with co-morbidities or limited life expectancy and risk of hypoglycemia.

Am J Kidney Dis. 2012;60(5):850-886.

- HbA1c will underestimate average blood glucose in patient on maintenance haemodialysis , and this should ideally be using an **HPLC based assay**.

- **Glycated albumin (GA)** may assess glycaemic control over a shorter time period (15–20 days) and with greater accuracy in patients with diabetes on MHD.

Correction factor for HbA1c measurement in patients on dialysis[6]

Haematocrit	Treatment with erythropoietin	Adjustment for HbA1c
≥30%	–	HbA1c × 1.14
<30%	Low dosage	HbA1c × 1.19
<30%	High dosage	HbA1c × 1.38.

- The use of self monitoring of blood glucose (**SMBG**) remains a **cornerstone** of the assessment of glycaemic control in patients with diabetes on maintenance haemodialysis who are being treated with agents that increase the risk of hypoglycaemia.

- **CGM** can provide an accurate assessment of glucose control and has been shown to be a reliable indicator of real-time blood glucose concentrations in both the general population, and in people with type 2 diabetes on MHDx.

Anti diabetic therapy in CKD

Non-insulin and insulin preparations in CKD and dialysis patients.

CLASS	DRUG	RELIABLE USE IN CKD	USE IN DIALYSIS
Biguanide	Metformin	sCre≤ 1.5 mg/dl in men sCre≤1.4 mg/dl in women	NO
Sulfonylureas	Glipizide	eGFR>45 ml/min/1.73m²	NO
	Gliclazide	eGFR>45 ml/min/1.73m²	NO
	Glimepride	eGFR>60 ml/min/1.73m²	NO
Meglitinides	Repaglinide	eGFR>30 ml/min/1.73m²	YES
	Nateglinide	eGFR>30ml/min/1.73m²	NO
Glitazone	Pioglitazone	eGFR>60 ml/min/1.73m²	NO
Alpha-glucosidase inhibitors	Acarbose	eGFR>60ml/min/1.73m²	NO
GLP-1 analogs	Exenatide	eGFR>30ml/min/1.73m²*	NO
	Linaglutide	eGFR>60 ml/min/1.73m²	NO
DPP-4 inhibitors	Sitagliptin	eGFR>30ml/min/1.73m² with dose adjustment	NO*
	Vildagliptin	eGFR>50ml/min/1.73m²*	NO
	Saxagliptin	eGFR≥50ml/min/1.73m² 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%

Insulin therapy in diabetic patient with CKD

- Insulin and insulin analogues can be used in all stages of CKD.
- In CKD, insulin action can change **individually** in an **unpredictable** manner; therefore, general advice on dose adjustments cannot be given.

Insulin requirements in patients with diabetes and progressive renal disease

- It is frequently noted that insulin requirements follow a **biphasic course** in progressive renal disease:
- In early stages of renal impairment, **resistance** to the effects of insulin predominates and may worsen, leading to a greater requirement for insulin.
- In more advanced renal impairment, the **loss of clearance** of insulin will lead to falling insulin requirement, and subsequently, a higher risk of hypoglycemia if insulin or sulfonylurea is not reduced.
- In addition, uremia induced **reduction in calorie intake** may also occur, leading to significant reductions in insulin requirement.
- A so-called "**burnt-out diabetes**" phenomenon has been described.

DOSING

- There was no statistically significant difference in insulin aspart (IAsp) doses across different stages of eGFR (<60 mL/min, 60–80 mL/min, >90 mL/min),
- while there was a reduction in lispro and human insulin dose in patients with eGFR < 60 mL/min.
- Moreover, insulin degludec (IDeg) did not reveal any significant difference in the absorption or clearance in subjects with renal impairment when compared to individuals with normal kidney function.
- The dose requirement of Detemir and Glargine was shown to be reduced up to 27% and 30% in patients with GFR < 60 mL/min.
- There is no published evidence related to the use of premix insulin in CKD patients.

Duke University Medical Center Glycaemic Safety Committee

- No dose modification was suggested in patients with CKD stages 1 & 2.
- prompt adjustments with reduction of 30%, 50% and 60% are often necessary in total daily dose depending on the CKD stages 3, 4 and 5 respectively.

Expert group recommendation 1: Dosing and Titration of Insulins in CKD
Recommendation on Dose Titration

GFR (mL/min/1.73 m^2)	% Reduction of TDD
>60	No Reduction
60–15	25%
<15	50%

diabetes research and clinical practice 127(2017)10–20

Glycemic regulation and haemodialysis

- Renal impairment leads to a net reduction in insulin requirement as increases in insulin resistance and reduced insulin secretion are offset by reduced renal insulin clearance.
- Reductions in total insulin requirements parallel reductions in eGFR, with a reduction in insulin requirement of about **50%** when eGFR falls to <15 mL/min.

The process of hemodialysis has a number of effects on glycemic control

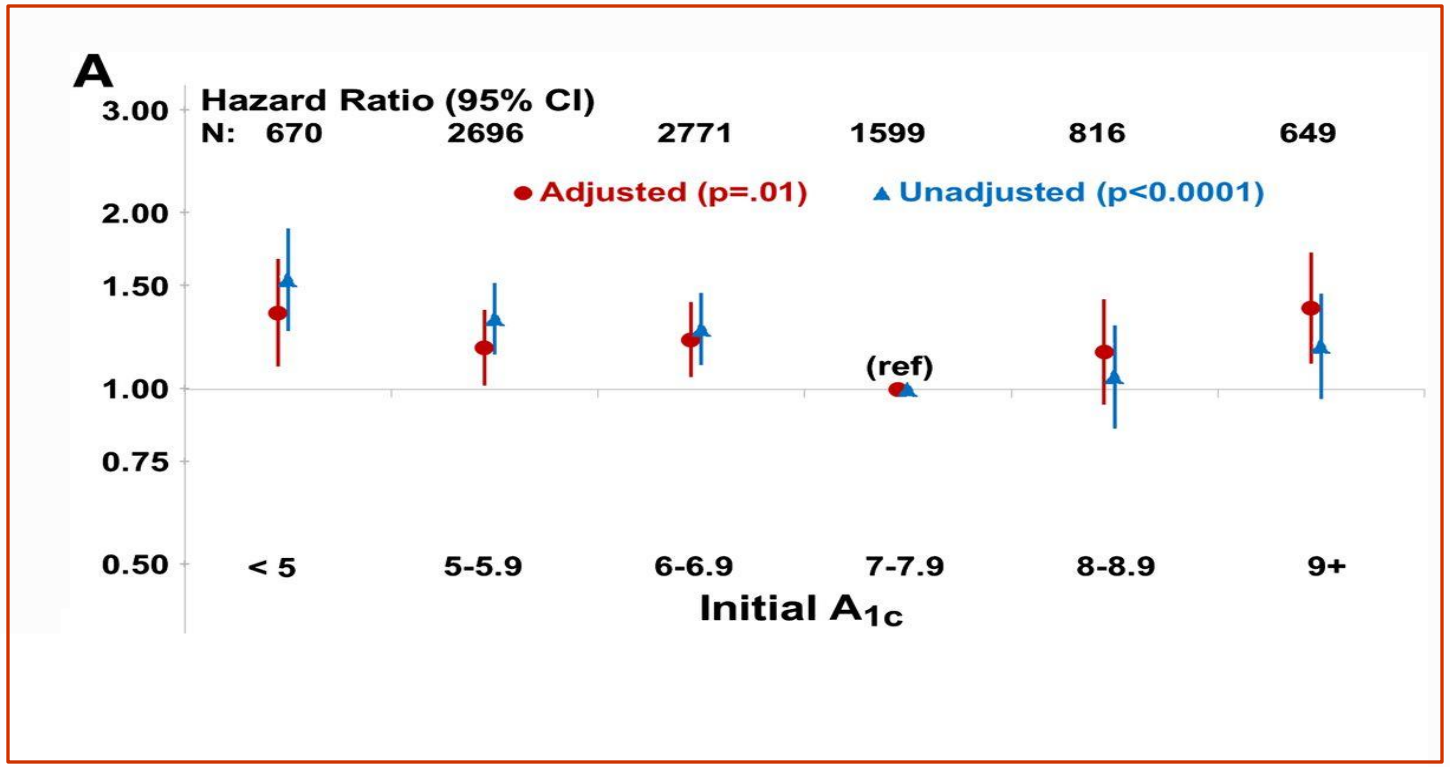
- HD effectively clears a number of **glucoregulatory** hormones, including insulin, C-peptide and glucagon.
- HD may **affect insulin secretion, clearance, and resistance** as the result of periodic improvement in uraemia, acidosis, and phosphate metabolism.
- **Glucose concentration in the dialysate** may also influence glucose control, with lower glucose dialysates being associated with hypoglycemia.
- Dialysis may **affect the clearance of antidiabetic therapy**.

Glycemic target in patients with diabetes on maintenance hemodialysis (MHDx)

- Patients with diabetes are at a particularly high risk and the overall survival on MHDx in patients with diabetes is about half that of their non-diabetic peers (**3.7 vs. 7 years**).
- The aim of glycaemic therapy in patients on MHDx should be to enhance quality of life, and to reduce extremes of glycaemia.

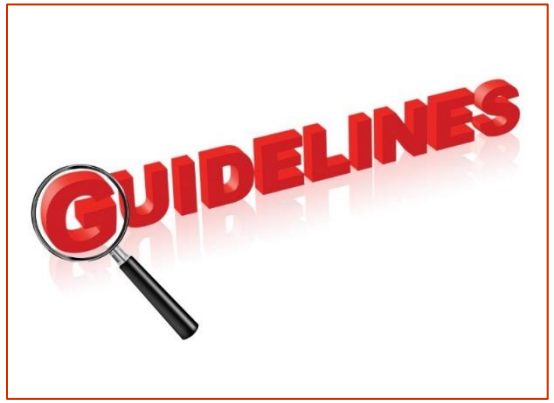
UK Renal Registry. 2014 – The Seventeenth Annual Report. Available at *https://www.renalreg.org/reports/2014-seventeenth-annual-report/* (accessed Feb 2016)

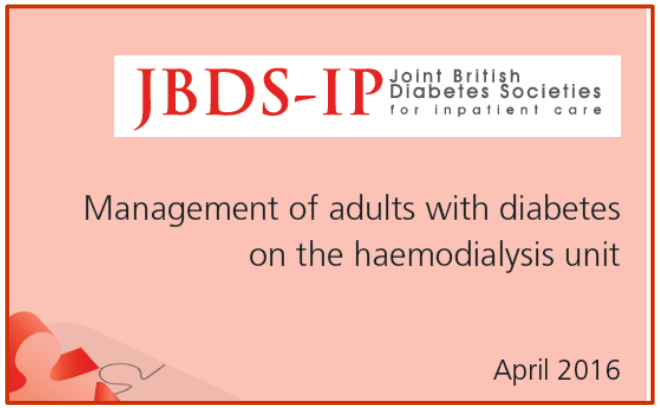
Risk of mortality in patients with diabetes and ESRD.



Evidence from observational studies suggests a **"U" shaped curve** of glycemic control in patients on MHDx, with one study suggesting a lowest mortality seen at HbA1c **7.0–7.9%**.

Katherine R. Tuttle et al. Dia Care 2014;37:2864-2883





- **Recommendations for glycemic control:**

- The target for HbA1c in patients with diabetes and on maintenance haemodialysis should be individualised but if the patient is on a hypoglycaemia inducing treatment should be aimed at between **7.5–8.5%**.
- It is likely that HbA1c of **9.5%** represents poor glycaemic control unless there is severe iron deficiency.
- Reduction in treatment should be considered for patients with HbA1c **7.5%** on potentially hypoglycaemia inducing agents.

ABCD
Association of British Clinical Diabetologists

THE RENAL ASSOCIATION
founded 1950

Managing hyperglycaemia in patients with diabetes and diabetic nephropathy-chronic kidney disease

Summary of recommendations

2018

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Endorsed by:
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DIABETES UK
KNOW DIABETES. FIGHT DIABETES.

Glycaemic targets in patients with diabetes and DN-CKD

	Glycaemic target	Note
Type 1 diabetes	48–58 mmol/mol (6.5–7.5%)	Younger patients within 10 years' duration of diabetes and variable microalbuminuria–CKD stage 2
	58–62 mmol/mol (7.5–7.8%)	The majority of patients with proteinuria and/or CKD stages 3–4
	58–68 mmol/mol (7.5–8.5%)	Patients with CKD stage 5-dialysis
Type 2 diabetes	48–58 mmol/mol (6.5–7.5%)	For the majority of patients who are aged <40 years, or have CKD stages 1–2 (no basis to aim for <52 mmol/mol (6.9%) unless the patient is aged <40 years and has CKD stages 1–2)
	52–58 mmol/mol (6.9–7.5%)	For those with CKD stages 3–4 this target may be appropriate with a GLP-1–SGLT-2 inhibitor-based treatment regime without insulin
	58–68 mmol/mol (7.5–8.5 %)	For those with CKD stages 3–4-proteinuria who are on an insulin-based regime, and those with CKD stage 5 who are on dialysis

Insulin regimen options in patients with diabetes on MHD

- **Recommendation :**
- If patients have troublesome hypoglycemia on NPH insulin, conversion to **analogue** insulins may be of benefit.
- Most patients on dialysis would benefit from **reduction of insulin doses during and immediately following dialysis** ,although advice should be individualized ideally on the basis of **CGM** data.
- **Basal bolus regimes** may be most flexible and best suited to the glycemic variability seen in patients with diabetes on MHD.
- In patients who are less likely to be able to comply with the requirements of a basal bolus regime consideration should be given to once daily regimes with **longer acting insulins**.
- **Biphasic** insulin regimens may be more difficult to manage on haemodialysis.

Joint British Diabetes Societies for inpatient care 2016

MANAGEMENT OF HYPERGLYCAEMIA IN HOSPITAL/SATELLITE DIALYSIS UNIT

- Patients should be encouraged to monitor and manage their own diabetes as far as possible
- **Patients should bring their own insulin/tablets with them to the Dialysis Unit**
- In patients on agents that could cause hypoglycaemia – blood glucose should be checked **pre dialysis** and **just before finishing dialysis**
- Blood glucose can fluctuate during dialysis **and most frequently drops in the last hour of dialysis**
- **Reduce total insulin dose by 10–15% during and immediately following dialysis**
- **Reduction in insulin dose (or oral hypoglycaemic agent) is required in those with HbA1c <58 mmol/mol (7.5%) to avoid hypo**

On rapid acting insulin:

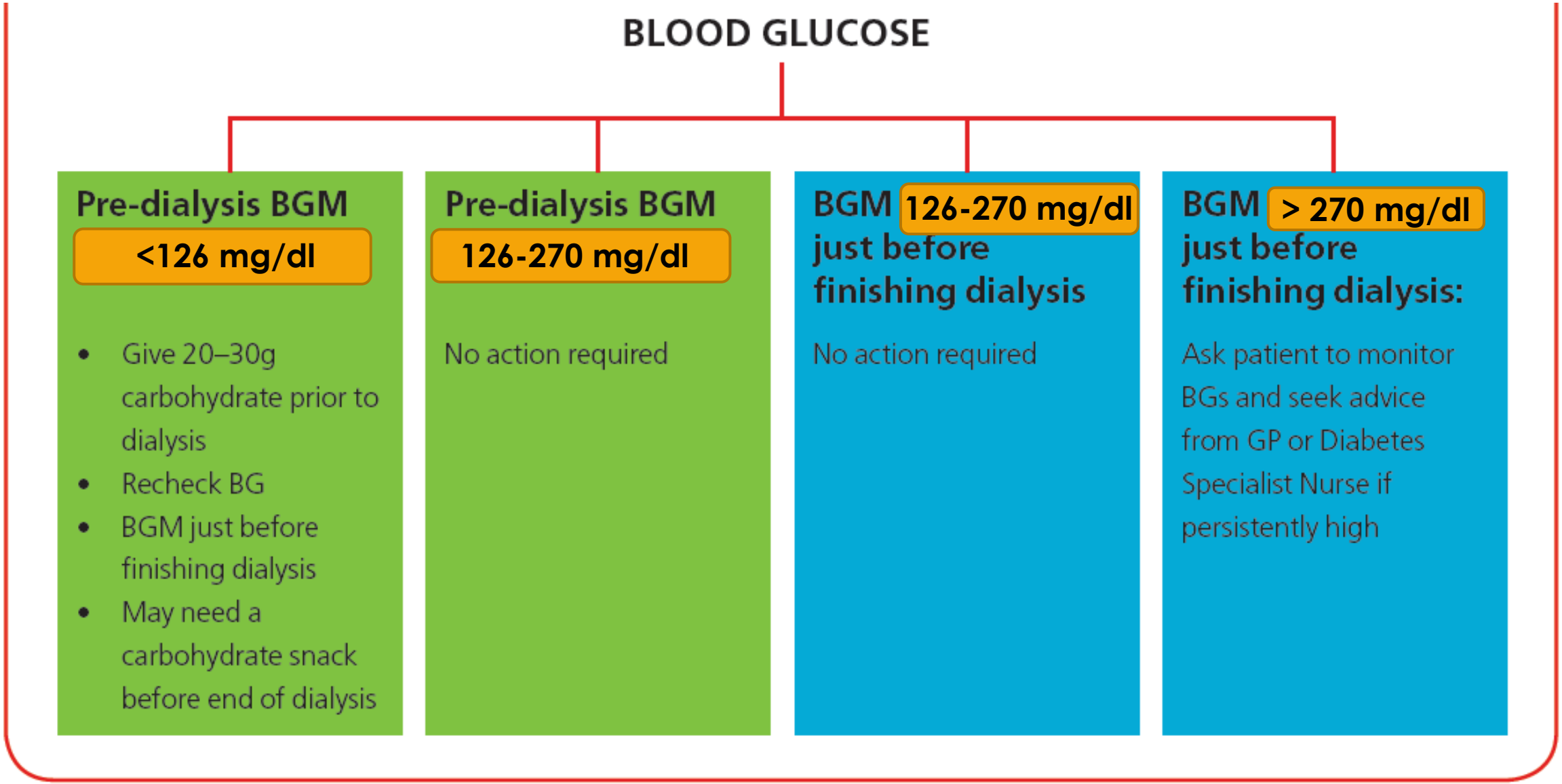
Patients should **reduce their usual breakfast (if morning dialysis), lunchtime (if afternoon dialysis) or evening insulin (if evening dialysis) by 10–15%** at the start of each shift

On premixed/biphasic insulin:

Patients should **reduce dose by 10–15%** with breakfast (morning and afternoon dialysis) and with their evening meal (if starting evening dialysis)

On long acting insulin:

Patients should **reduce dose by 25%** in the morning or in the evening of dialysis



Joint British Diabetes Societies for inpatient care 2016

Insulin regimen options in patients with diabetes on peritoneal dialysis

- Many peritoneal dialysis patients will require insulin therapy to achieve adequate glycemic control. For such patients, use of subcutaneous, rather than intraperitoneal, insulin is recommended .
- The initial dose of insulin should be decreased by approximately 50 percent.

Clin Invest Med. 2012;35(3):E132-43

Hypoglycemia in MHD

- **Recommendation:**

In managing patients with diabetes on MHD, clinicians should be aware of the significantly increased risk of hypoglycemia caused by:

- • Poor or erratic nutritional intake.
- • Reduced clearance of endogenous or exogenous insulin by the kidney and the liver.
- • Decreased hepatic gluconeogenesis.
- Patients with diabetes on MHD should be adequately counselled on the increased risk of hypoglycemia and that hypoglycemia can occur with **diminished classical symptoms**.
- Patients on maintenance hemodialysis on active treatment of diabetes with insulin or oral hypoglycemic agent(s), should have **capillary glucose assessed pre- and post-dialysis.**

Summary

- The increasing prevalence of diabetes mellitus (DM) is recognized as a leading cause of chronic renal failure (CRF) and end stage renal disease (ESRD).
- The optimal glycaemic target should also be determined as per the GFR value.
- SMBG should be the preferred choice, however, CGMS may be considered if patients can afford.
- The requirement of insulin shows a biphasic course ,so insulin doses in CKD to be reduced with lower eGFR levels.
- HbA1c aproximatly 7% in different stages of CKD and 7.5% - 8.5% for MHD is preferred.
- Special care and management would be need for diabetic patients on PD or MHD.

Key massage

Implementation of an optimized metabolic control improves not only the course of the nephropathy, but also the prognosis of patients.

The management of the patients with DKD, preferably treated with insulin, calls for close collaboration between the multidisciplinary team consisting of nephrologists, endocrinologists, nutritionists, and nurses.

Despite, insulin being considered as the most effective therapeutic regimen in DKD patients, its prescription need frequent reassessment for individualization, adjustment and titration of doses in accordance with the eGFR.

In addition, special attention should be given to the intensification of glycemic control along with monitoring of hypoglycemia.


Thank you