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Research Article

Management of type 2 Diabetes in patients with Chronic Kidney Disease

hypoglycaemia increases as a result of accumulation of these drugs and their metabolites.

In a retrospective analysis of 240,000 subjects, the incidence of hypoglycemia was higher in patients with CKD versus without CKD. Among patients with diabetes, the rate was 10.72 versus 5.33 per 100 patient-months and among patients without diabetes was 3.46 versus 2.23 per 100 patient-months, for CKD versus no CKD, respectively. The odds of 1day mortality were increased at all levels of hypoglycemia (6). This excessive mortality associated with hypoglycemia makes this a significant threat to patients with CKD.

Patients with prolonged diabetes have attenuated autonomic response to hypoglycemia which is known as hypoglycemia unawareness. This is especially seen in patients with diabetes mellitus type 1. Such patients may not manifest classical autonomic symptoms of hypoglycemia like sweating, tremors and hunger; in such cases, neuroglycopenic symptoms may develop only when blood glucose level drops to lower than 50 or 40mg/dl. These include weakness, dizziness, decreased concentration, seizures or unconsciousness. An episode of hypoglycemia may decrease the manifestations for next few days or weeks, and hence make the patient more prone to further unrecognized episodes of hypoglycemia, which may ultimately lead to a severe episode with loss of consciousness. The risk of hypoglycemia has been shown to be higher at night and is more likely to go unrecognized while patient is sleeping. Hence nocturnal hypoglycemia should be carefully avoided e.g. by keeping insulin doses low at night and watched for by checking a midnight or 2am blood glucose once in a while.

Target glycemic control

There are no set recommendations regarding target blood glucose levels needed to prevent progression of nephropathy, prevention of other micro vascular complications, and reduction of cardiovascular events and mortality. Although Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend glycosylated hemoglobin (HbA1c) targets similar to patients without kidney disease i.e. less than 7%, the current concepts are changing after the Action to Control Cardiovascular Risk in Diabetes (ACCORD) and Action

Introduction

About 30–40% of patients with chronic kidney disease (CKD) patients also have concomitant diabetes (1). Diabetes has been shown to have significantly stronger association with CKD in patients with younger age (2). Diabetes management in CKD poses significant challenge because of the increased risk of hypoglycaemia, renal excretion of most oral antidiabetics, variable appetite of patients with CKD and the effects of hemodialysis and peritoneal dialysis on glycemic control. Management of diabetes after renal transplantation is a separate entity with different challenges due to the effect of immunosuppressants especially steroids on carbohydrate metabolism and will not be discussed in this review.

CKD and hypoglycaemia

There are several factors which predispose patients with CKD to an increased risk of hypoglycaemia:

- Patients with decreased GFR (<60 ml/min per 1.73 m²) due to diabetes and CKD have decreased insulin requirement as insulin is cleared by kidneys. (3)
- In CKD patients the peripheral metabolism of insulin is reduced (4).
- With decrease in glycogen storage in the patients with CKD and uremia due to suboptimal nutrition anorexia may occur (5).
- There occurs less renal gluconeogenesis as a result of reduction in renal mass in CKD patients (4).
- Most of the medications used for treating diabetes are excreted by kidneys from the body. In CKD incidence of

in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation (ADVANCE) trials in non CKD patients (7, 8). The latter showed that tight glycemic control in elderly patients, or in patients with prolonged diabetes or other co morbidities, might not be beneficial. In fact, such an approach may increase mortality. It is believed that the excess morbidity and mortality shown with aggressive glycemic control might be due to hypoglycemia.

An HbA_{1c} of less than 7% in patients with CKD stages 3 and beyond might be associated with risk of hypoglycemia in patients on insulin or sulphonylureas.

Patients with diabetes and CKD are at high risk for cardiovascular events and mortality. Several observational studies have shown conflicting results regarding the association of HbA_{1c} and mortality as to which level is most beneficial. A recent study by Rick et al demonstrated that HbA_{1c} between 7 to 7.9% was associated with lowest mortality. The death hazard ratio increased at higher and lower HbA_{1c} categories. Similarly, the mortality was lowest for average blood glucose of 150 to 175mg/dl, death hazard ratio increasing for both higher and lower average blood glucose readings (9).

However, the use of HbA_{1c} and its association with glycemic control has been questioned in patients with CKD. Glycosylated haemoglobin (HbA_{1c}) is used to assess glycemic control in patients with diabetes, because it reflects average glucose values over approximately previous 3 months. However in patients with CKD, HbA_{1c} might not reflect glycemic control accurately due to several factors including shorter red blood cell lifespan, hemodialysis, iron deficiency, recent blood transfusions, accelerated erythropoiesis due to erythropoietin therapy and acidosis. Additionally, there is formation of carbamylated haemoglobin in the presence of elevated urea, which can interfere with HbA_{1c} measurement using column and ion-exchange chromatography and agar gel electrophoresis (10). However, in patients on dialysis, HbA_{1c} was found to underestimate the glycemic control in one study (11); while in patients with HbA_{1c} more than 7.5% it was found to be overestimating glucose control (12).

These observations however, may be not clinically relevant in most patients not requiring dialysis. Morgan et al reported that in non dialysis CKD patients, HbA_{1c} is reflective of glycemic control similar to patients without kidney disease (11).

However, at present, HbA_{1c} is the best available marker of glycemic control available to us to evaluate glycemic control in patients with CKD.

Similarly, self monitoring or point of care capillary blood glucose testing using some meters can be affected by isodextrin and maltose in peritoneal dialysis fluid and hence further complicates the management.

Oral antidiabetic agents in CKD (Table 1)

Sulphonylureas commonly used today include glimepiride, glipizide and gliclazide. Though all of these are predominantly metabolised by liver, only glimepiride has active metabolites which are renally excreted while glipizide and gliclazide have inactive metabolites. Therefore glipizide and gliclazide are the preferred sulphonylureas of choice in CKD patients (13).

Although repaglinide elimination half life is marginally increased in CKD, this can be safely used in CKD patients without dose modification (13).

Thiazolidinedione use has reduced nowadays with reports of cardiovascular mortality with rosiglitazone (14) and possibly bladder carcinoma with pioglitazone, although the latter is an unproven association (15). Both these drugs do not accumulate in patients with CKD, but they can cause edema and heart failure (16). Hence their use is best avoided in CKD patients.

Alpha glucosidase inhibitors i.e. acarbose, miglitol and voglibose are absorbed to some extent and renally excreted (13). In addition, alpha-glucosidase inhibitors are rarely accompanied by hypoglycemia and are administered without dose adjustments in dialysis patients. However, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines recommended that alpha-glucosidase inhibitors should be avoided in patients with advanced stage CKD and on dialysis. Furthermore, mitiglinide is not currently used in the US(13).

Metformin

Metformin is the oldest and most widely prescribed oral antidiabetic. Metformin use has been shown to be associated with reduced cardiovascular risk and mortality. It rarely causes hypoglycemia if used alone and is weight neutral.

However U.S. Food and Drug Administration prescribing guidelines for metformin contraindicate its use in men and women with serum creatinine concentrations ≥ 1.5 and ≥ 1.4 mg/dL (≥ 132 and ≥ 123 $\mu\text{mol/L}$) respectively. These recommendations stem from the fear generated by phenformin (the first drug of this same class) induced lactic acidosis (16).

Metformin is excreted from kidneys and drug levels may increase in patients with CKD.

Recently, large scale metaanalyses have shown that lactic acidosis is extremely rare in patients on metformin (4.3 per 100,000) and the incidence is not different from those on other glucose lowering drugs (5.3 per 100,000) (17). Hence the causal relation of metformin with lactic acidosis is not known.

Data from observational studies suggest that metformin is safe in patients with mild and moderate CKD or even perhaps beneficial due to reduction in cardiovascular mortality.

In view of this new outlook on metformin and the fact that creatinine alone is not a marker of renal status, the guidelines for metformin use have been modified by various organisations to use eGFR cut offs rather than creatinine cut offs (table 2). Metformin can be safely given in patients with mild renal insufficiency; dose modification has been suggested for moderate renal insufficiency and renal function should be done frequently. It is prudent to avoid metformin in severe renal insufficiency with eGFR less than 30ml/min.

In Indian settings, the low cost of treatment, absence of hypoglycemia and poor accessibility of insulin to a large chunk of population makes metformin use a good option (18).

Table 1: Dosing Adjustments for Drugs Used to Treat Hyperglycemia by CKD Stage.

| Class | Agent | Dosing Recommendation | |
|---------------------------------|--|--|---|
| | | CKD Stage 3-5 | CKD Stage 5D |
| First-generation sulfonylureas | Acetohexamide | Avoid | Avoid |
| | Chlorpropamide | Reduce dose by 50% with GFR < 70 and ≥ 50 mL/min/1.73 m ² ; Avoid when GFR < 50 mL/min/1.73 m ² | Avoid |
| | Tolazamide | Avoid | Avoid |
| | Tolbutamide | Avoid | Avoid |
| Second-generation sulfonylureas | Glipizide | Preferred sulfonylurea No dose adjustment necessary | Preferred sulfonylurea No dose adjustment necessary |
| | Glyburide | Avoid | Avoid |
| | Glimepiride | Initiate at low dose, 1 mg daily | Avoid |
| Alpha-glucosidase inhibitors | Acarbose | Not recommended in patients with SCr > 2 mg/dL | Avoid |
| | Miglitol | Not recommended in patients with SCr > 2 mg/dL | Avoid |
| Biguanides | Metformin | Contraindicated with kidney dysfunction defined as SCr ≥ 1.5 mg/dL in men or ≥ 1.4 mg/dL in women | Avoid |
| Meglitinides | Repaglinide | No dose adjustment necessary | No dose adjustment necessary |
| | Nateglinide | Initiate at low dose, 60 mg before each meal | Avoid |
| Thiazolidinediones | Pioglitazone | No dose adjustment necessary | No dose adjustment necessary |
| | Rosiglitazone | No dose adjustment necessary | No dose adjustment necessary |
| Incretin mimetics | Exenatide | No dose adjustment necessary | No dose adjustment necessary |
| | Liraglutide ¹⁸ | No dosage adjustment necessary (limited experience in patients with renal impairment; use with caution) | No dosage adjustment necessary (limited experience in patients with renal impairment; use with caution) |
| Amylin analog | Pramlintide | No dose adjustment necessary for GFR 20-50 mL/min/1.73 m ² | No data available |
| DPP-4 inhibitor | Sitagliptin | Reduce dose by 50% (50 mg/d) when GFR < 50 and ≥ 30 mL/min/1.73 m ² and by 75% (25 mg/d) when GFR < 30 mL/min/1.73 m ² | Reduce dose by 75% (25 mg/d) |
| | Saxagliptin ¹⁷ | 2.5 mg/d | 2.5 mg/d |
| | Linagliptin | 5mg/d | 5mg/d |
| | Vildagliptin | 50mg/d | 50mg/d |
| Insulin preparations | Rapid-acting <ul style="list-style-type: none"> Regular Lispro solution Aspartate solution Glulisine | Doses not specified by level of kidney function but should be adjusted based on frequent monitoring to balance goals of glycemic control while avoiding hypoglycemia. Other considerations not specific to level of kidney function include avoiding or minimizing interactions with drugs used to lower blood glucose, eg, saxagliptin (not studied in patients taking insulin) | |
| | Intermediate-acting: isophane insulin suspension (NPH) | | |
| | Long-acting <ul style="list-style-type: none"> Glargine Detemir | | |

CKD = chronic kidney disease; DPP-4 = dipeptidyl peptidase-4; GFR = glomerular filtration rate; SCr = serum creatinine, SGLT2 = sodium-glucose cotransporter2

DPP IV (dipeptidyl peptidase-4) inhibitors

There are four approved DPP IV inhibitors available in Indian market; sitagliptine, vildagliptine, saxagliptine and very recently approved linagliptine.

Mechanism of action: In response to nutrient ingestion, the gastrointestinal tract secretes hormones called incretins, of which GLP1 and GIP are two important incretins that have been studied. These hormones stimulate beta cells to secrete insulin and reduce glucagon secretion apart from a plethora of other effects on gastrointestinal emptying, satiety, and probably

increasing beta cell mass. Deficiency of these hormones is also regarded as of the contributory mechanisms for development of type 2 diabetes. These hormones, however, are subject to rapid degradation by an enzyme called DPP IV. Hence, DPP-4 inhibitors provide another avenue for glycemic control by preventing degradation of GLP1 and GIP.

Since the effect of these drugs is glucose dependent, they do not cause hypoglycemia which is an advantage in patients with CKD.

Sitagliptine, vildagliptine and saxagliptine are



predominantly excreted renally. Therefore in moderate and severe renal insufficiency dose modification is recommended (table 3) (18).

Only 7% of Linagliptine is excreted in urine, hence no dose modification is recommended in any stage of renal insufficiency (19).

GLP 1 analogues

Liraglutide, exenatide, lixisenatide, albiglutide and dulaglutide are analogues of GLP1 which are resistant to DPP IV.

GLP1 analogues can be used in early stages of renal dysfunction, but they are contraindicated in CKD stage 4-5. Exenatide dose needs to be adjusted if eGFR is between 30-50 ml/min/1.73m². Lixisenatide should be carefully administered with monitoring of renal function in CKD stage 2-3. Liraglutide, albiglutide and dulaglutide can be given in CKD stage 2-3 without dose adjustment.

Renal outcomes of liraglutide were analysed in LEADER trial and revealed that liraglutide resulted in lower rates of the development and progression of diabetic kidney disease than placebo (20). Similarly, semaglutide reduced the rate of composite renal outcome that by 36% as compared to placebo (21) and lixisenatide significantly reduced urinary albumin excretion over a period of 2 years (22).

SGLT2 inhibitors

This new class of antidiabetic drugs reduces blood glucose

by inhibiting sodium glucose cotransporter type 2 in kidneys, thus causing glycosuria. These drugs also reduce blood pressure and cause weight loss. There are three molecules currently available- canagliflozin, dapagliflozin and empagliflozin. Two large trials CANVAS and EMPA-REG have shown impressive cardioprotective data. Secondary analysis of these have shown renoprotective effects, including markedly lower rates of decline in the estimated GFR in addition to lower rates of albuminuria.

The use of SGLT-2 inhibitors should be considered in patients up to CKD stage 2, in view of their ability to prevent progression of kidney dysfunction and also to reduce cardiovascular risk which is a major concern in CKD patients. Dose reduction has been suggested in CKD stage 3-5 stage, and therapy should be discontinued (CKD stage 4-5) (23,24).

However, it is to be noted that all these drugs have limited efficacy and insulin is ultimately required for most patients with CKD stage 3 and beyond.

Insulin

There are several types of insulins available (table 4) and various insulin regimens can be used.

There are some peculiarities with insulin use in CKD patients. While on one hand, CKD is associated with increased insulin resistance and some patients require very high doses of insulin in initial stages; on the other hand, in patients with advanced stages of CKD, there is decreased insulin degradation which results in marked reduction or even cessation of insulin therapy in some patients with CKD.

How to start insulin in a patient with CKD

The usual starting total daily dose (TDD) for insulin should be low usually 0.1 to 0.3 units per kg body weight depending upon the nutritional status or frailty of the patient. In frail patients and in patients with poor appetite, 0.2 or lower units/kgbw should be used. However, some obese patients might require doses as high as 1.2 to 1.5 units /kgbw (25).

The best insulin regimen to be used is multiple doses of insulin (MDI) or basal bolus regimen wherein patient receives rapid acting insulins before meals and a long action basal

Table 2: Proposed recommendations for use of metformin based on eGFR.

| eGFR level (mL/min per 1.73 m ²) | Action |
|--|---|
| >60 | No renal contraindication to metformin Monitor renal function annually Continue use |
| 60-45 | Increase monitoring of renal function (every 3-6 months) Prescribe metformin with caution |
| 45-30 | 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 | Stop metformin |

Table 3: Clearance of Available DPP-4 Inhibitors by Kidneys and Their Recommended Doses in Patients with Renal Insufficiency

| Parameter | Sitagliptine | Vildagliptine | Saxagliptine | Linagliptine |
|---|--|--|---|--|
| Approximate proportion of drug excreted in urine, % | 79 | 23 unchanged, 85 total | 75 | <7 |
| Dose adjustment in renal insufficiency | Can be used in full dose (100 mg QD) in mild renal insufficiency. In moderate renal insufficiency, the recommended dose is 50 mg QD. In severe renal insufficiency and in patients requiring dialysis, the recommended dose is 25 mg QD. | Can be used in full dose (50 mg BID) in mild renal insufficiency. In patients with moderate or severe renal insufficiency or with ESRD, the recommended dose is 50 mg QD. | No dose adjustment (2.5 mg QD or 5 mg QD) is needed in mild renal insufficiency. In moderate and severe renal insufficiency and in patients receiving hemodialysis, the recommended dose is 2.5 mg QD. | No dose adjustment is needed in any stage of renal failure |

Mild renal insufficiency, CrCl ≥ 50 mL/min.

Moderate renal insufficiency, CrCl ≥ 30 to ≤ 50 mL/min.

Severe renal insufficiency, CrCl < 30 mL/min.

Abbreviations: BID, twice daily; CrCl, creatinine clearance; ESRD, end-stage renal disease; QD, once daily.

Table 4: Insulin preparations: Considerations in hemodialysis patients.

| INSULIN PREPARATION | ONSET OF ACTION | PEAK ACTION | EFFECTIVE DURATION | DOSING CHANGE IN RENAL FAILURE |
|----------------------------------|-----------------|-------------|--------------------|---|
| Rapid-acting | | | | Reduce dose by 25% when glomerular filtration rate (GFR) is 10–50 mL/min, and by 50% when GFR < 10 mL/min |
| Regular | 30–60 min | 2–3 hr | 8–10 hr | |
| Lispro (Humalog) | 5–15 min | 30–90 min | 4–6 hr | |
| Aspart (NovoLog) | 5–15 min | 30–90 min | 4–6 hr | |
| Long-acting | | | | Reduce dose by 25% when GFR is 10–50 mL/min, and by 50% when GFR is less than 10 mL/min |
| Neutral protamine Hagedorn (NPH) | 2–4 hr | 4–10 hr | 12–18 hr | |
| Glargine (Lantus) | 2–4 hr | None | 20–24 hr | |
| Detemir (Levemir) | 3–4 hr | 3–14 hr | 6–23 (19.9) hr | |
| Premixed | | | | Reduce dose by 25% when GFR is 10–50 mL/min, and by 50% when GFR is less than 10 mL/min |
| 70/30 human mix | 30–60 min | 3–12 hr | 12–18 hr | |
| 70/30 aspart mix | 5–15 min | 30–90 min | 12–18 hr | |
| 75/25 lispro mix | 5–15 min | 30–90 min | 12–18 hr | |

insulin at bedtime. It has been observed that the requirement of insulin before dinner is usually low or absent and therefore minimum possible dose should be given at this time to avoid nocturnal hypoglycemia. The usual starting doses would be

- Before breakfast- lispro or aspart or glulisine or regular insulin- 0.2 X TDD
- Before lunch- lispro or aspart or glulisine or regular insulin- 0.2 X TDD
- Before dinner- lispro or aspart or glulisine or regular insulin- 0 to 0.1 X TDD
- Bedtime – glargine or detemir 0.4X TDD

The doses should be titrated after monitoring glucose values before meals and bedtime. The rule of thumb to prevent nocturnal hypoglycemia is- “Bedtime glucose should always be higher than before dinner glucose by atleast 40mg/dl”.

However, most patients prefer premixed insulin twice a day before breakfast and dinner because it is more convenient. It has also been observed that one can avoid or use minimal insulin before dinner, and only once a day premixed insulin may suffice in many CKD patients. The starting doses would be

- Before breakfast- premixed insulin {e.g.novomix (30/70) or humalog mix (25/75) or mixtard (30/70) or huminsulin (30/70)}- TDD X 0.8
- Before dinner- premixed insulin {e.g.novomix (30/70) or humalog mix (25/75) or mixtard (30/70) or huminsulin (30/70)}- TDD X 0 to 0.2

The doses should then be titrated as per self monitoring of blood glucose.

It is important to stress the use of self monitoring of blood glucose in all patients on insulin and counsel them regarding glycemic targets of about 100 to 140mg/dl fasting and less than 200mg/dl postmeal or random.

In patients on hemodialysis, insulin resistance may decrease due to uremia. Rapid insulin degradation continues, and hence

the insulin requirement reduces at the time of dialysis. Some patients require half the doses on dialysis days and some do not require any insulin. However, some patients will continue to need the same insulin dose even on dialysis days, and hence, the doses should be individualised by patient to patient basis (26,27).

In patients on continuous ambulatory peritoneal dialysis (CAPD), glucose in the peritoneal fluid gets absorbed leading to hyperglycemia even in patients without diabetes occasionally. Insulin can be administered either subcutaneously or intraperitoneally to manage this type of hyperglycemia with careful titration of doses depending on the amount the timing of CAPD (28).

Conclusion

Diabetes mellitus coexists in more than a third of CKD patients. Patients with CKD are prone to antidiabetic induced or even spontaneous hypoglycemia. Therefore the recommended glycemic targets are HbA1c of 7 to 7.9% which optimally reduces cardiovascular risk. The choice of antidiabetics to achieve these targets depends on stage of CKD, appetite, cost of therapy and patient convenience.

- Stage of CKD- most antidiabetics can be safely continued in CKD stages 1 and 2; while in stages 3 and beyond insulin is the preferred agent. Glipizide, gliclazide, DPP IV inhibitors can be cautiously given with dose modification. Linagliptine can be given at all stages without dose modification.
- Appetite- in patients with uremia and anorexia, oral antidiabetics should be avoided and insulin is the first choice.
- The use of metformin should be guided by eGFR and not serum creatinine. Metformin can be continued without dose modification till eGFR of 45ml/min and with dose reduction till 30ml/min. The risk of lactic acidosis with metformin is minimal or absent.
- Insulin regimens to be used are

- Rapid acting analogues before each meal (reduced dose before dinner) and long acting insulin once a day (usually bedtime). The doses to start with are
- total daily dose (TDD) =weight X 0.1 or 0.3
- TDD X 0.4 as basal
- TDD X 0.2 before breakfast and lunch and TDD X 0 or 0.1 before dinner
- Premixed insulin before breakfast (TDD X 0.8) and before dinner (TDD X 0 to 0.2).

Additional caution is required in patients at risk for acute kidney injury or with anticipated significant fluctuations in renal status, based on previous history, other comorbidities, or potentially interacting medications.

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