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Medicine

GLYCEMIC MANAGEMENT IN CHRONIC KIDNEY DISEASE (CKD) PATIENTS

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KEYWORDS :

INTRODUCTION

The antecedent to end-stage renal disease (ESRD) is chronic kidney disease (CKD). Dialysis or medical management or kidney transplant is the preferred treatment course for ESRD depending on the disease stage. Normally, kidneys are involved in performing various functions, viz., removing toxins from the blood, blood pressure control, body acid-base balance, fluidic balance, maintaining normal hemoglobin through production of erythropoietin, vitamin D regulation, and minerals and electrolytes balance, that includes sodium, potassium, calcium, phosphorus, magnesium (link, 2016). Thus, evaluating kidney function is critical, especially in patients with CKD risk factors (Table 1).

Table 1. Risk factors for developing CKD (Link, 2016)

S. No	Risk factor
1	Age > 60 years
2	Diabetes
3	Hypertension
4	Cardiovascular disease (CVD)
5	Family history of CKD
6	History of autoimmune disease
7	History of recurrent urinary tract infections
8	Nephrolithiasis
9	Kidney cancer
10	Systemic infections
11	Abnormal serum creatinine (SCr), low glomerular filtration rate (GFR), or previous acute kidney injury (AKI)
12	Organ transplant (use of anti-rejection drugs, which are nephrotoxic)

Amongst all the risk factors, Diabetes mellitus, being a global epidemic, is a major cause of CKD. Diabetes nephropathy is the most common complication related to diabetes that affects almost 20–40% of diabetic individuals (Hahr and Molitch, 2015). With the progression in kidney malfunction, multifactorial alterations including altered insulin clearance and insulin resistance, contribute to changes in glucose/insulin homeostasis in CKD. Glucose homeostasis and insulin resistance disparity result in anomalous glycemic control in CKD patients. Few of the factors that contribute to imbalance in glucose homeostasis that eventually results in insulin resistance in CKD include (Williams and Garg, 2014) -

- Accumulation of uremic toxins,
- Chronic inflammation,
- Excess visceral fat,
- Oxidative stress,
- Metabolic acidosis, and
- Vitamin D deficiency

This in turn, increases the risk of cardiovascular disease in patients with CKD. In CKD patients, glomerular filtration rate (GFR) decreases to less than 15 to 20 ml.min^{-1} per 1.73 m^{2} resulting in reduced renal insulin clearance. Concurrently, there is a lower insulin production and increased insulin resistance (Kovesdy et al., 2008). Alterations in insulin metabolism have been linked to the accumulation of uremic toxins. Improved insulin sensitivity on dialysis suggests the role of uremic toxins in CKD. Altered adipose tissue secretion pattern in CKD is an important cause of pro-inflammatory molecules that results in insulin resistance. Oxidative stress-mediated production of pro-inflammatory molecules in adipose tissue, a feature of uremia, and erythropoietin deficiency also contribute to insulin resistance (Garg and Williams, 2013).

CRITERIA FOR ESTABLISHING CKD

As per Kidney Disease Improving Global Outcomes (KDIGO) 2012 guidelines, CKD is considered to be present if one or more of the following criteria/condition occurs for more than three months-

- A persistent and progressive reduction in GFR to less than 60 ml.min^{-1}per1.73 m^{2}.
- Albuminuria ≥ 30 mg in 24 hours or urine albumin to creatinine ratio (UACR) ≥ 30g.mg^{-1}
- Urine sediment abnormalities (i.e., hematuria or red cell casts)
- Electrolyte and other tubular disorders
- Histological abnormalities
- Structural abnormalities (viz., polycystic kidney)
- History of kidney transplant

Kidney function is determined by calculating the GFR, which requires the patient'sage, race, sex, and serum creatinine level. Normal GFR is 90 ml.min^{-1} or greater. After the age of 40, there is a loss of 8 ml.min^{-1} for each decade in GFR. Amount of albuminuria determines the stage of CKD (Link, 2016).

INDICATORS OF GLYCEMIC STATE

Hyperglycemia is the chief cause of diabetic kidney disease. Hence, to delay /prevent the onset of diabetic complications, glycemic control is indispensable (Williams and Garg, 2014). Glycemic control in CKD patients is complex and requires detailed knowledge of safe drugs and their metabolism in the diseased kidney. Furthermore, based on diseased state, individualization of the glycemic target for each patient is also required. The standard measure for glycemic control is Hemoglobin A1c (HbA1c) index. ADA recommends HbA1c target for diabetes control to be less than or around 7 % (Hahr, and Molitch, 2015). In 2007, KDOQI guidelines for Diabetes and CKD suggested a target HbA1c of <7.0 % (KDOQI, 2007) however, in 2012 guideline was revised and recommend an HbA1c of ~7.0 % (KDOQI, 2012). Lower HbA1c levels are coupled with high risk of hypoglycemia that may cause cardiac complications, seizure, stroke or death. Malnourished, weak and elderly, people with erratic eating habits, on insulin and sulfonylureas, and with CKD are at higher for this (Kalantar-Zadeh, 2012). Although, HbA1c can be erroneous in some patients with kidney disease. Alternatively, Fructosamine and glycated albumin levels can be used to estimate glycemic control (Freedman, 2012). Glycation of multiple serum proteins can be indicated by fructosamine levels, whereas the specific glycation of albumin is reflected by glycated albumin levels (Freedman et al., 2010).

Maintenance of glycemic levels is critical in CKD patients. In CKD patients GFR is < 60 ml.min^{-1} per 1.73 m^{2}, the risk of hypoglycemia is augmented. This is attributed to decreased clearance of hypoglycemic agents and reduced gluconeogenesis by the kidney. Simultaneously, there is a decrease in insulin clearance as well. Thus, dose adjustment and glycemia management become critical with each CKD patient (Tuttle et al., 2014).

THERAPEUTIC MANAGEMENT OF GLYCEMIA IN CKD:

Traditionally, Insulin has been considered to be the safest anti-diabetic agent in renal failure. However, there has been development of novel and safer oral noninsulin agents or oral hypoglycemic agents (OHA). Patients of type 1 diabetes mellitus accompanied with CKD require insulin, while, patients of type II diabetes mellitus with progressive renal dysfunctioning need change in pharmacotherapy with the decline of GFR (Yadav, 2012).

A. Insulin therapy in CKD patients

ß pancreatic cells of a healthy non-diabetic person secrets about 0.5

U/kg/day (50% of the daily requirement), irrespective of blood glucose levels. While remaining 50% of the requirement is released post-prandially. In a non-diabetic person, kidney is not much involved in the disposal of the insulin. However, disposal of exogenous insulin administered in diabetic patient is primarily carried out by the kidneys. Ironically, once the GFR reduces < 20ml.ml^{-1}, insulin clearance is distinctly reduced. This is further aggravated by uremia. As a result, patients with CKD have elevated basal levels of insulin (Mak and DeFronzo, 1992).

Consequently, a biphasic insulin therapy is required in diabetic patients with renal disease. Initially, such patients have higher insulin requirement owing to insulin resistance. Typically, basal insulin requirement is fulfilled by intermediate- or long-acting insulin formulations and nutritional requirement is by supplied by short- or rapid-acting insulin. However, once the renal condition deteriorates, (with creatinine clearance < 60 mL/min), insulin therapy has to be either withdrawn or reduced significantly (Adrogu, 1992).

For this reason, in order to minimize the risk of hypoglycemia in CKD, therapy individualization and regular monitoring followed by requisite adjustment of insulin dose, are critically essential. Thus, insulin therapy in CKD patients requires both long acting as well as short acting insulin based on their GFR and glycemic state. Insulin glargine or Neutral Protamine Hagedorn (NPH) insulin are the recommended long-acting insulin to be used in conjunction with a short-acting (regular) or fast-acting insulin analogue such as lispro or insulin (Freeman et al., 1992). Further insulin dose should be titrated and individualized based on glycemic state of the patient. A premixed insulin preparation is considered to be a convenient choice to basal prandial combinations; however this premixed insulin is inflexible and does not suffice the requirement of therapy individualization in CKD patients (Yadav, 2012).

B.Noninsulin glucose-lowering agents or oral hypoglycemic agents (OHA)

Noninsulin glucose-lowering agents are considered to be suitable for patients with CKD.These agents not only reduces the risk of hypoglycemia associated with insulin in CKD patients but also improves the patient compliance by reducing the psychological stress associated with parenteral administration of insulin. However, OHA have renal excretion primarily, hence renal function evaluation is a prime requisite prior to initiation of OHA therapy. Thus, a selection of OHA is primarily dependant on the stage of CKD (Yadav, 2012).

a. Sulfonylureas

Sulfonylureas promote insulin release from the pancreatic β cells resulting in the lowering of blood sugar levels. However, sulfonylureas depend on β-cell reserves for the insulin release. Hence, patients with prolonged diabetes often respond poorly to sulfonylureas as they have poor β-cell reserves of insulin. Also, the glucose-lowering effect of sulfonylureas is not dependent on levels of glucose. Consequently, sulfonylureas can result in unregulated insulin release and thereby increasing the risk of hypoglycemia (Schejter et al., 2012). Long-acting sulfonylureas (e.g., glyburide and chlorpropamide) often result in life-threatening hypoglycemia and hence not recommended for CKD patients (Holstein et al 2003). Nevertheless, shorter-acting drugs that are metabolized in the liver, viz., glipizide and glimepiride are considered to be reasonably safe and can be administered to CKD patients (Kalantar-Zadeh et al., 2012).

b. Biguanides

Metformin is an insulin sensitizer that acts mainly in the liver. Thus, it does not cause hypoglycemia. However, as per current U.S. Food and Drug Administration (FDA) prescription guideline, Metformin is contraindicated, in men with serum creatinine ≥1.5 mg.dl^{-1} and in women with a serum creatinine ≥1.4 mg.dl^{-1}. Metformin can predispose to lactic acidosis and therefore should be used cautiously in patients with impaired lactic acid metabolism and excretion (Runge et al., 2009). Metformin has been reported to deteriorate kidney function and further aggravate problems in the presence of CKD (Pongwecharak, 2009).

c. Thiazolidinediones

Pioglitazone and Rosiglitazone are the two widely used thiazolidinediones**.** They act on skeletal muscle and adipose tissue, peroxisome proliferator-activated receptor γ (PPAR-γ) receptors, and thereby improve insulin sensitivity. These agents are considered safe in CKD and patients on hemodialysis therapy as they do not increase the risk of hypoglycemia. However, all thiazolidinediones are reported to result in fluid retention that may cause heart failure (Schneider et al., 2008; Nissen, 2007).

d. α-Glucosidase Inhibitors

Alpha-glucosidase inhibitors include acarbose and miglitol. These agents decrease the breakdown oligo-and disaccharides in the small intestine thereby delaying glucose absorption after a meal. These agents majorly exhibit GI side effects such as bloating, flatulence, and abdominal cramping. These agents lower HbA1c levels by 0.5–0.8 % and do not affect body weight (Nathan et al., 2009). However, these drugs are contraindicated in patients with serum creatinine levels > 2 mg.dl^{-1}as they may result in liver failure.

e. Dipeptidyl peptidase-4 (DDP-4) inhibitors (Gliptins)

DDP-4 inhibitors reduce the breakdown of incretin hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Thus, these agents prolong the action of incretin hormones which in turn increases insulin secretion and decreases glucagon secretion. The agents of this class include Sitagliptin, Saxagliptin, Linagliptin, and Alogliptin.

This class of medication decreases HbA1c by 0.5–0.8 % and does not affect body weight. DPP-4 inhibitors are majorly disposed via kidneys, except for linagliptin which is excreted via hepatobilary route. These drugs generally don't require dose adjustment in patients with mild renal impairment (CrCl>50 ml/min). Gliptins are contraindicated in diabetic ketoacidosis and as therapy for type 1 diabetes mellitus. Due to better tolerability and lower risk of hypoglycemia, these drugs are a popular choice for glycemia management in CKD (Chan et al., 2008).

f. Sodium-glucose co-transporter 2 (SGLT2) inhibitors

Glucose absorption from the kidney is reduced by SGLT2 inhibitors, resulting in an increase in glucose excretion and reduction in HbA1c by 0.9–1.0 %.Canagliflozin and Dapagliflozin are the two currently used SGLT2 inhibitors. These agents can result in weight loss due to the increase in urine glucose output (Kalra, 2014).

g. Meglitinides

Mechanistically, these agents are similar to sulphonylureas. However, they are shorter acting and their effects are more glucose-level dependent. These agents have a low risk of hypoglycemia. Repaglinide and Nateglinide are two drugs from this category of actives (Devineni et al., 2013).

h. Other oral medications

Bromocriptine (dopamine receptor agonist) and Colesevelam (bile acid sequestrant) are also used for the glycemic management; however, detailed investigational reports of these drugs in CKD are not available.

i. Other subcutaneous medications

i).Glucagon-like peptide 1 (GLP-1) Receptor Agonists

These agents mimic gut hormones, incretins, thereby increasing the insulin release. Exenatide (regular and extended-release) and liraglutide are GLP-1 receptor agonist that are administered via the parenteral route. These agents delay glucagon secretion and gastric emptying. These agents also affect the satiety center resulting in weight loss (Davidson, et al., 2011).

ii). Amylin analog

Pramlintide, an injectable medication, is the amylin analog. Amylin is secreted along with insulin by pancreatic β-cells. These analogs are used as an adjunct to insulin therapy in both type 1and type 2 diabetes. It generally reduces HbA1c by 0.5–1.0 % and there is no dose adjustment required in CKD (Epocrates Online).

C. Dietary modifications

Incorporating dietary management in CKD along with therapy has been found to avoid or improve complications associated with CKD viz., acidosis, hyperkalemia, hyperphosphatemia and uremic symptoms and CKD progression. Restricted protein diet intakes are recommended for CKD patients. This may range from protein intake of ~0.6 g/kg/day (low-protein diets) to as low as 0.3 g/kg/day (extreme restrictions) depending on CKD and its complications especially acidosis status (Garneata et al., 2016). In order to reduce/ prevent metabolic acidosis in CKD inclusion of sodium bicarbonate supplements or more simply, inclusion of fruits and vegetables has been found to be effective. While, lowering the intake of sodium chloride as well as phosphates by avoiding junk and processed food

has been found to have renal protective effect. Dietary modifications have been found to control proteinuria and slow renal function decline (Mitch and Remuzzi, 2016).

CONCLUSION:

CKD is one of the most common and progressive disease, especially in diabetic patients. Glycemic management in CKD is a challenging task. Glycemic control impedes diabetic kidney disease progression in its early stages. A good glycemic control preserves the renal function and decreases the secondary complications like, cardiac complications. Goals for glycemic control need to be frequently and constantly monitored and readjusted in CKD patients. Insulin has been conventionally used for glycemic management; however there has been advancement in glycemic management with the development of newer and safer noninsulin glucose-lowering agents. An undervalued aspect of CKD management is dietary management. Low-sodium intake, low protein intake and increase of fruits and vegetable along with low-cost anti-diabetic or reno-protective drugs can be an effective way to manage CKD especially in underdeveloped and developing countries with economic constraints. However, there is a need for extensive and in-depth randomized controlled trials of these currently available drugs and concurrent dietary modifications. This will help to establish a rational and effective therapeutic management of glycemia in CKD patients that will help to preserve kidney function in such patients for a prolonged period of time.

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