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Overcoming Challenges of Glycaemic Management in Diabetic Patients with Kidney Disease

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ABSTRACT

A common occurrence encountered in clinical practice is the patient with hyperglycaemia and chronic kidney disease (CKD). Many times there are challenges with achieving and/or maintaining stable glycaemic control with patients' blood glucose swinging from hyperglycaemia to hypoglycaemia. There is alteration in glucose homeostasis in patients with worsening kidney disease due to decreased renal and hepatic clearance of insulin, decreased renal gluconeogenesis, poor dietary intake, increased half-life of insulin, loss of body weight and fat mass, decreased levels of cathecolamines, effects of dialysis and presence of other co-morbidities. HbA1c in spite of some limitations is still regarded as a good long-term measure of glycaemic control in patients with progressive renal failure, especially in well dialysed subjects. Although not finally settled, a HbA1c target between 7-8% (or fasting blood glucose of 120-140 mg/dl) would be appropriate during treatment. Insulin is the most commonly used anti-hyperglycaemic drug once renal failure has set in. This is probably because the drug does not have deleterious effect on the kidney per se, and it is easier to titrate for stabilization or withheld if hypoglycaemia occurs. Treatment should be individualized in every case based on such factors like age of the patient, duration of diabetes, stage of kidney disease and whether on renal replacement therapy (RRT) or the type of RRT. Among the non-insulin drugs, extreme caution is indicated in the use of metformin because of its potential to cause lactic acidosis. Most of these drugs require dose adjustment in the context of advancing renal failure. As far as glycaemic management is concerned low protein diet still has a beneficial effect in diabetic patients with renal failure.

INTRODUCTION

A common occurrence encountered in clinical practice is the patient with hyperglycaemia and chronic kidney disease (CKD). The kidney condition may have resulted from diabetes or from other aetiology. Indeed diabetes is now the leading cause of End Stage Renal Disease (ESRD) in industrialized countries[1]. Diabetes is also now a leading cause of CKD in Nigeria[2]. Many reports indicate higher co-morbidity and poorer outcomes among diabetic patients undergoing dialysis compared with non-diabetics [3,4]. In the US, approximately two-thirds of patients die within 5 years of initiating dialysis[5]. The mortality rate is even higher in low-resource countries like Nigeria because very few are able to afford regular dialysis. Many times there are challenges with achieving and/or maintaining good glycaemic control. It is not uncommon for a patient's metabolic state to swing between hperglycaemia and hypoglycaemia. Both metabolic states can be injurious to the well-being of these patients. The objective of this review is to highlight the various challenges encountered in managing patients with both diabetes and CKD particularly in resource-poor countries like ours, and suggest ways in which they can be overcome.

Importance of good glycaemic control

Large scale randomised intervention trials have demonstrated that good glycaemic control prevents

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the development of microvascular complications such as retinopathy, peripheral neuropathy and nephropathy in diabetic patients [6, 7]. In the UKPDS (United Kingdom Prospective Study), more intensive glycaemic control resulted in a 33% reduction of microalbuminuria and clinical grade nephropathy at 12 years[8]. Duration of diabetes and levels of HbA1c were the only significant risk factors for nephropathy and retinopathy in 269 Swedish type 1 diabetic patients[9]. Optimal glucose control also slows down the rate of progression of these complications once they have set in. Evidence showed that maximal benefits of good glycaemic control are seen in those with microalbuminuria compared with macroalbuminuria[8]. Indeed once overt or clinical proteinuria has set in, improved glycaemic control may not be beneficial.

Altered glucose homeostasis in patients with diabetes mellitus and CKD

In these patients, glucose levels can be at any of end of the spectrum- hyperglycaemia or hypoglycaemia. Abnormal glucose tolerance and fasting hyperglycaemia has been observed in patients with progressive kidney disease, particularly those receiving haemodialysis, even in the absence of pre-existing diabetes[10]. On the other hand many patients with established diabetes and advancing CKD have a reduced insulin requirement and frequently suffer hypoglycaemia during course of renal disease[11-12]. There are many reasons for these alterations in glucose homeostasis in patients with worsening kidney disease. This include decreased renal and hepatic clearance of insulin, decreased renal gluconeogenesis, poor dietary intake, increased half-life of insulin, loss of body weight and fat mass, decreased levels of cathecolamines, effects of dialysis- both haemodialysis and peritoneal dialysis treatment and presence of other co-morbid conditions[13]. The effects of the diminished insulin resistance is somewhat mitigated by a concomitant decrease in insulin secretion, probably due to hyperparathyroidism and activated Vitamin D deficiency[14-15].

What glycaemic targets should be aimed at in patients with diabetes mellitus?

Krolewski and co-workers in a study among patients with type 1 reported that increasing microalbuminuria was noticed from HbA1c of 8.1% upwards[16]. The DCCT landmark study however indicated a continuous reduction in the risk of diabetic nephropathy as the HbA1c levels fell[17]. The number of subjects with hypoglycaemia however increased in the DCCT study the stricter the HbA1c target aimed at. The American Diabetes Association and the American Association of Clinical Endocrinologists recommended <7% and <6.5% respectively as HbA1c targets in their guidelines. The ADA in particular advised a less strict HbA1c target for patients with reduced life expectancy[18]. Recently the ACCORD (Action to Control Cardiovascular Risk in Diabetes) Trial researchers in a study designed to test the hypothesis that diabetic patients with additional cardiovascular risk factors who underwent intensive glucose treatment had less cardiovascular end-points, reported increased mortality in patients with intensive arm[19]. Bearing in mind that many diabetic patients with chronic kidney disease fit this description, it is reasonable to be cautious in setting glycaemic targets for these patients. HbA1c target between 7-8% are considered acceptable for patients with diabetes mellitus on chronic dialysis. Where facilities are not available for HbA1c testing like in our environment, the fasting blood glucose, ranging between 120-140 can reasonably be used as a corresponding guide.

Definition and stages of CKD

Kidney disease is said to be present when there is either structural damage to the kidneys as shown by e.g. albuminuria, or GFR is d"60mls/min/1.73m^2. Accordingly, 5 stages of CKD are clearly defined (see table1)[20]. In stages 1 and 2 where the GFR is greater than 60mls/min/1.73m^2, there is usually little alteration in the glucose homeostasis. In diabetic patients who also have CKD with stages 3-5 (GFR is <60mls/min/1.73m^2) there is increased risk of

Table 1: Definition and stages of kidney disease

Stage	Definition
Stage 1	Normal GFR (greater than 90 mL/min per 1.73 m2) and persistent albuminuria
Stage 2	GFR between 60 to 89 mL/min per 1.73 m2 and persistent albuminuria
Stage 3	GFR between 30 and 59 mL/min per 1.73 m2
Stage 4	GFR between 15 and 29 mL/min per 1.73 m2
Stage 5	GFR of less than 15 mL/min per 1.73 m2 or end-stage renal disease

hypoglycaemia or worsening hyperglycaemia. This is due to alterations in glucose metabolism and pharmacokinetics of anti-diabetic agents. Glycaemic monitoring and stabilization can be quite challenging for patients in these stages.

Monitoring glycaemia in CKD patients with diabetes

Monitoring diabetic patients with progressive CKD poses significant challenges. Haemoglobin A1c is widely accepted as the best measure of long-term glycaemic control in patients with diabetes. During their lifespan of about 120 days, the haemoglobin chain in the red blood cells is exposed to carbohydrate molecules in the blood. There is progressive adduction of glucose to HbA the degree of which corresponds to the level of glucose concentration in the blood. Among the minor fractions of HbA1, i.e. a, b and c, HbA1c is the largest fraction and also demonstrate consistently the ambient concentration of glucose milieu. Thus a standard measure of HbA1c could be used to assess level of glycaemic control over a period of 2-3 months. As a result of sustained effort at standardizing assays of HbA1c, recently, the test is now recommended not only for monitoring but also for diagnosis of diabetes[21-22]. However the use of HbA1c in diabetic patients with CKD is confounded by formation of carbamylated haemoglobin, metabolic acidosis and other possible factors (see table 2)[23-24].

Table 2: Haemoglobin A1c confounders in CKD patients with diabetes

1. Carbamylation of haemoglobin
2. Metabolic acidosis
3. Frequent blood transfusion
4. Shortened erythrocytes lifespan
5. Erythropoietin-induced accelerated erythropoiesis

These limitations notwithstanding, HbA1c is still considered as a good long-term measure of glycaemic control in patients with progressive renal failure, especially in well dialysed subjects[25-26]. The problem in Nigeria like many other countries of Africa is that HbA1c is not available in most health care facilities. Since the relationship between HbA1c and prevalent retinopathy (a microvascular complication of diabetes like nephropathy) is similar to that of plasma glucose, fasting and 2-hour plasma glucose can still be reasonably used as a measure of monitoring in these patients[27].

Other alternative markers of long-term monitoring proposed include fructosamine and glycated albumin. Fructosamine, which is formed by a non-enzymatic reaction between the carbonyl group of glucose and amine group of protein has been found to correlate well with mean blood glucose and HbA1c[28]. However fructosamine is not available for routine clinical use and can only reflect glycaemic state in a shorter period of 2 or 3 weeks compared with HbA1c. In addition fructosamine may also be unreliable in patients with renal failure[25, 28]. Glycated albumin has been shown to be superior to HbA1c[29-30]. Its use is however limited in peritoneal dialysis and there is no clear consensus regarding its therapeutic target level for glycaemic control.

Treatment with hypoglycaemic agents

Non-insulin drugs:

More options are now available for oral hypoglycaemic treatment of diabetic patients. In our environment, sulphonylureas and metformin are still widely used for treating hyperglycaemia in patients with diabetes. The metabolism or excretion of these drugs to varying extent involves the kidneys, so there is need for careful consideration in the choice of use of any non-insulin based drug. Most of these drugs require dose adjustment in the context of advancing renal failure (as shown in table 3). Extreme caution is indicated in the use of metformin because of its potential to cause lactic acidosis. Perhaps its use should only be considered for CKD patients in stages 1-2. The administration of sulphonylureas in patients with chronic kidney disease requires careful attention to dosing and the routes of elimination. There is a significant risk of profound hypoglycemia with the use of sulphonylureas in patients with end stage kidney disease. Thiazolidinediones (TZDs) are relatively new class of hypoglycaemic agents. They enhance insulin sensitivity at the sites of action of insulin through binding to peroxisome proliferator activated-receptor (PPAR-¥). The most notable side effect of these agents is hepatotoxity because their majorly metabolized in the liver. In fact the first drug in this class- troglitazone- was withdrawn on account of severe hepatotoxity. The newer agents such as Rosiglitazone and Pioglitazone are much less hepatotoxic. They also cause weight gain and oedema through accumulation of fat and fluid; hence they are

Table 3: Dosage-adjustment of common anti-hyperglycaemic agents in CKD patients with diabetes

Class	Mechanism of action	Medication	Adjustment/Restriction in CKD
Biguanides	Decreases hepatic glucose production and intestinal glucose, increases insulin sensitivity, possibly through activation of AMP-activated protein kinase	Metformin (Glucophage)	Contraindicated with renal impairment because of potential severe lactic acidosis[a]
Sulfonylureas	Insulin secretagogues, through binding to(and thus closure of) the KATP channel in the pancreatic beta cells	Glibenclamide (Daonil)	CrCl >50:avoid use
		Glimepiride (Amaryl)	Renal impairment: start 1mg daily, increase slowly and monitor glucose[b]
		Glipizide (Glucotrol	CrCl>50 decrease dose 50% dosing in RRT not defined
		Chlorpropamide (Diabinese)	CrCl >50:decrease dose 50%CrCl>50: avoid
		Gliclazide	Reduce dose in severe renal insufficiency
Meglitinides	Non-sulfonylurea insulin secretagogues binding to(and thus closure of) the K_{ATP} channel in the pancreatic beta cells	Repaglinide	CrCl 20-40:start 0.5mgbefore each, through meal, titrate with cautions : CrCl <20:not defined
		Nateglinide	No adjustment: dosing in RRT not defined
Alpha-glucosidase	Block enzymatic degradation of complex. Carbohydrates in the gut, through inhibition of intestinal alpha-amylase and membrane- bound intestinal alpha –glucosidase hydrolase enzymes	Miglitol	Cr> 2mg/dl: avoid use·
		Acarbose	Cr> 2mg/dl: avoid use
Thiazolidinediones	Increased insulin sensitivity through PPAR-gamma activation	Pioglitazone HCL	No adjustment; dosing in RRT not defined
		Rosiglitazone	No Adjustment HD/CAPD: no supplement
DDP-4 inhibitor	Increase in insulin synthesis/release and decreases In glucagon synthesis, through slowing of Incretin metabolism	Sitagliptin phosphate	CrCl 30-50:50mg qd;CrCl<30:25mg qd;HD/CAPD:no supplement
Incretin mimetic	Stimulation of insulin secretion in a Glucose-specific manner, inhibition of gastric Emptying, suppression of glucagon secretion, and central anorexic activity	Exenatide	CrCl 30-80:no adjustment ; CrCl<30:
Insulin	Adjustment/restriction in CKD. Replaces/supplements endogenous insulin	Various formulations and brands	Half-life may be prolonged and dose reduction may be necessary

PPAR- Peroxisome proliferator-activated receptor; RRT- Renal replacement therapy; DPP- Dipeptidyl peptidase.
[a]Degree of renal impairment remains undefined.
Adapted with modification from Kovesdy et al[39]

not advisable in patients with heart failure or renal patients with significant fluid retention. However pharmacokinetics of TZDs do not change with decreasing renal function and so no dose adjustment may be required in patients with chronic kidney disease.

I would suggest a little paragraph about use of Thiazolidinediones in CKD and potential dangers as well. While I agree they are less commonly used in Nigeria, these drugs are available and sold in the Nigerian drug market.

On the other hand there is little or no need for dose adjustment with meglitinides, particularly nateglinide. It is still early to know the effect on the kidney of a novel hypoglycaemic drug, Sodium-Glucose co-transporter inhibitor (dapagliflozin and sergliflozin), which hopefully will soon be licensed for clinical use[31]. These agents lower blood glucose by increasing renal excretion of glucose[32]. Moreover they do not induce insulin secretion, hypoglycaemia or weight gain[33].

Insulin:

Insulin is the most commonly used anti-hyperglycaemic drug once renal failure has set in. This is probably because the drug does not have deleterious effect on the kidney per se, and it is easier to titrate for stabilization or withheld if hypoglycaemia occurs. The reason for high rate of hypoglycaemia in patients with CKD on insulin therapy is because of the decrease in dose requirement as kidney function declines. It is difficult to generalize dosage and regime of insulin; treatment should be individualized in every case based on such factors like age of the patient, duration of diabetes, stage of kidney disease and whether on renal replacement therapy (RRT) or the type of RRT. Interestingly, administration of insulin through the peritoneum in patients receiving haemodialysis has been associated with better insulin sensitivity and fewer hypoglycaemic and hyperglycaemic episodes[34]. Patients treated with continuous ambulatory peritoneal dialysis or continuous cycler peritoneal dialysis (CAPD and CCPD) can be treated with intraperitoneal insulin. This regimen has some potential advantages; It provides a continuous insulin infusion. It eliminates the need for injections. It may provide a more physiologic route of absorption, since the exogenous insulin is absorbed into the portal vein which mimics the action of pancreatic insulin. However adverse conditions including peritonitis and low HDL cholesterol have been reported in intraperitoneal delivery of insulin[35-36].

Dietary Measures

Traditionally these patients are placed on protein restriction but accumulating evidence has not supported the usefulness of this measure in management of decline in renal function[37-38]. In a meta-analysis involving eight randomised controlled trials, Yu Pan and co-workers showed that a change in weight mean differences (WMD) for GFR or Creatinine Clearance was not significantly associated with low protein diet. However a decrease in WMD for HbA_{1c} was significant in the Low Protein Diet group ($P = 0.005$). Thus as far as glycaemic management is concerned low protein diet still has a beneficial effect in diabetic patients with renal failure. There is a need though, to balance this benefit against possible malnutrition caused by enhanced protein breakdown due to insulin deficiency.

Conclusion

Good glycaemic control is established as an essential strategy to prevent or slow down progression disease in patients with coexistent diabetes and kidney failure. However, management is associated with a number of challenges particularly with respect to glycaemic monitoring and the choice of, or handling of agents used for treating hyperglycaemia. In our resource-poor environment, these patients can still be effectively monitored with plasma glucose. There is need for careful consideration in choosing among the plethora of available non-insulin agents and, in particular, extreme caution is necessary in the use of metformin and sulphonylureas. Insulin treatment with an individualised approach based on the age of the patient, duration of diabetes and stage of kidney disease is probably the best mode of treatment of hyperglycemia.

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