

Management of hyperglycemia in patients with chronic kidney disease

Patrícia Aires Neto, Henrique Vieira Gomes, Mário Campos

Nephrology Department, Coimbra University Hospitals, Coimbra - Portugal

ABSTRACT

Diabetes currently accounts for approximately 45% of cases of end-stage renal failure in patients undergoing hemodialysis. Several observational studies have identified a positive correlation between measures of glycemic control and cardiovascular and microvascular benefits. Several randomized prospective studies have been conducted to quantify the impact of strict glycemic control on morbidity and mortality. These studies have consistently demonstrated an association between strict glycemic control and a reduction in microvascular events, but these results contrast with the lack of consistent results regarding macrovascular events. Treating diabetes has always been challenging. This challenge is increased in chronic kidney disease, due to changes in the pharmacokinetics and pharmacodynamics of insulin and most oral antidiabetic agents. The available pharmacotherapeutic arsenal for treating type 2 diabetes mellitus currently involves approximately 6 different pharmacological classes of oral antidiabetic agents and different modalities of insulin therapy.

Key words: *Chronic kidney disease, Diabetes mellitus, Treatment*

INTRODUCTION

The optimization of glycemic control in diabetes mellitus delays the onset of microvascular complications such as microalbuminuria and alleviates the decline in glomerular filtration rate (GFR). These results were demonstrated in the Diabetes Control and Complications Trial / Epidemiology of Diabetes (DCCT/EDIC) (1) study which was conducted in patients with type 1 diabetes mellitus and the

UK Prospective Diabetes Study (UKPDS) (2) and Kumamoto studies (3) regarding patients with type 2 diabetes mellitus. The randomized STENO-2 study (4) was designed to assess the effects of intensive multifactorial therapy (a low-fat diet, the use of angiotensin-converting enzyme [ACE] inhibitors, vitamins C and E, and aspirin as secondary preventative measures) and antidiabetic drug therapy in patients with type 2 diabetes mellitus and microalbuminuria, with a therapeutic target of glycated hemoglobin (HbA_{1c}) below 6.5%. The results showed that the patients in the intensive treatment group displayed delayed progression to nephropathy, retinopathy and diabetic autonomic neuropathy. The ADVANCE (5) study corroborated the known benefit associated with stricter glycemic control (defined by a target value of HbA_{1c} below 6.5%) based on the positive impact of limiting the onset and evolution of nephropathy in type 2 diabetes mellitus.

Uremia alone alters absorption by delaying gastric emptying and limiting the absorptive phase with respect to intestinal wall edema. Delayed gastric emptying can be reversibly aggravated by hyperglycemia (6), or it can result from gastroparesis in the context of diabetic autonomic neuropathy (7).

Drug distribution can be impaired by quantitative changes (hypoalbuminemia – nephrotic syndrome) or qualitative changes (drug displacement by accumulated acids or uremia-induced changes in albumin's tertiary and quaternary structures). These changes have particularly important implications in the presence of high levels of plasma protein binding, which is seen with oral antidiabetics (8).

Because no significant pharmacokinetic changes have been observed with the use of oral antidiabetics in chronic kidney disease (CKD) stages 1 and 2, the use of these drugs is considered safe (9). The treatment of type 2 diabetes mellitus can follow the current recommendations of the American Diabetes Association (ADA), which were made in early 2012 (10).

MONITORING GLYCEMIC CONTROL

Serial measurements of HbA_{1c} facilitate the monitoring of the effectiveness of antidiabetic therapy; however, there are some concerns and interference may arise regarding their dosage determinations in renal failure. Hemoglobin carbamylation, which occurs in uremia and metabolic acidosis, can be associated with false HbA_{1c} elevations (11). In contrast to the shortened lifespan of red blood cells, accelerated erythropoiesis due to the use of erythropoiesis-stimulating agents and frequent transfusions is associated with falsely normalized HbA_{1c} levels (11). Regardless of the limitations of measuring HbA_{1c}, this method is considered to be useful for monitoring glycemic control in renal failure.

Glycemic control should be considered adequate in diabetic patients undergoing hemodialysis when their fasting blood glucose levels are below 140 mg/dL, their postprandial blood glucose is below 200 mg/dl and their HbA_{1c} values fall between 6% and 7% for type 1 diabetes mellitus and between 7% and 8% for type 2 diabetes mellitus (12).

Shurraw et al carried out a retrospective cohort study with 1,484 patients to determine whether worse glycemic control as measured using serum glucose and HbA_{1c} level was independently associated with higher mortality in these patients. They found that higher casual glucose and HbA_{1c} levels were not associated with mortality in patients undergoing hemodialysis (13).

Recognizing the paucity and inconsistency of the data, published guidelines for glycemic control in dialysis patients are classified as “weak” in their evidence base and caution clinicians regarding the risk of hypoglycemia when following guidelines developed for the general population.

ABNORMALITIES IN CARBOHYDRATE AND INSULIN METABOLISM IN CKD

The kidney plays a central role in insulin clearance; 60% of renal insulin clearance depends on glomerular filtration, and the remainder depends on secretion from peritubular capillaries (14-17). Less than 1% of intact insulin is found in urine.

The liver is responsible for eliminating 50% of the portal insulin, and a significantly relevant first-pass effect exists. Insulin that is administered parenterally or subcutaneously is primarily eliminated by the kidney. This aspect is particularly relevant to the diabetic population experiencing renal failure while receiving insulin therapy (18).

Insulin degradation is only markedly impaired in severe renal dysfunction, when the GFR decreases to values below 15-20 ml/min; until this stage, decreased insulin degradation is compensated for by tubular secretion. Uremia reduces insulin degradation by the liver, but this condition can be reversed by instituting renal replacement therapy (18).

Increased insulin secretion can be observed under normal conditions with the purpose of normalizing plasma glucose. Reduced insulin pancreatic secretion (which is apparently related to metabolic acidosis) with secondary hyperparathyroidism is usually observed in CKD and interferes with the ability of pancreatic beta cells to secrete insulin (19).

MANAGEMENT OF HYPERGLYCEMIA IN PATIENTS WITH DIABETES AND CKD

Use of insulin

Prandial insulin preparations obtained through recombinant DNA techniques are currently available, and they are divided into short-acting human insulin (regular) and fast-acting insulin analogues (insulin lispro, aspart and glulisine). Intermediate-acting insulin (human) and long-acting analogues are available as basal insulin.

Studies of insulin therapy in different stages of CKD are quite limited (20). However, given the risk for hypoglycemia that is simultaneously accompanied by an increase in insulin resistance, fast-acting and long-acting analogues are preferred (21). Rave et al (22) conducted a study on a small population of type 1 diabetic patients with and without diabetic nephropathy and with and without renal failure, and they compared the differences in pharmacokinetics and pharmacodynamics between regular insulin and insulin lispro. The authors concluded that plasma insulin levels are higher and the metabolic response to regular insulin is lower in patients with diabetic nephropathy and renal failure. This result is in contrast to the stability and safety of insulin lispro with respect to its pharmacokinetic and pharmacodynamic properties in the same population. Aisenpreis et al (23) demonstrated that the pulsatile pharmacokinetic profile of insulin lispro may facilitate the correction of hyperglycemia and may reduce the risk of hypoglycemic events, which is particularly important for the type 1 and 2 diabetic population undergoing hemodialysis.

Toyoda et al (24) demonstrated that in 14 hemodialysis undergoing patients who were being treated with neutral prot-

amine Hagedorn (NPH) based basal-bolus insulin therapy, regular insulin, NPH insulin or premixed insulin and who were switched to glargine, an improvement in quality of life and a reduction in frequency of hypoglycemic episodes occurred. Dose adjustments may be necessary based on the degree of kidney dysfunction: There is no need to perform dose adjustments when the GFR is above 50 ml/min. A 25% dose reduction is required when the GFR is between 10 and 50 ml/min, and a 50% reduction is necessary when the GFR is below 10 ml/min (25).

Protocols for intraperitoneal insulin administration in patients undergoing peritoneal dialysis are described in the literature (26).

ORAL HYPOGLYCEMIC AGENTS

Sulfonylureas

First-generation sulfonylureas (SFUs) are contraindicated in CKD. Glibenclamide is a long-acting, second-generation SFU; it is preferentially metabolized by the liver, yielding 2 renally excreted metabolites with hypoglycemic activity. As a result, several pharmacokinetic parameters increase with chronic use. Based on these factors, this SFU should be avoided in CKD stages 3-5 of renal failure (27).

Glipizide is an SFU that is rapidly and completely absorbed, although absorption can be slightly impaired by the presence of food. Its maximum concentration is achieved within 90 to 120 minutes of administration, allowing for increased insulin secretion in the postprandial period (28). The average elimination half-life is 1-5 hours. Glipizide is a fast- and short-acting SFU that is completely metabolized in the liver. Few pharmacokinetic studies have been conducted on patients with renal failure. Glipizide excretion is independent of renal function because it is completely metabolized by the liver; however, metabolic accumulation can be observed with prolonged half-life (creatinine clearance of 6 hours at 30 ml/min and 12 hours at 20 ml/min). According to recommendations of the National Kidney Foundation Disease Outcomes Quality Initiative (KDOQI), this SFU is safe and requires no dose reduction in any stage of renal failure (29).

Glimepiride is characterized by rapid and complete absorption, increased plasma protein binding and a small distribution volume. It is completely metabolized by the liver and preferentially excreted through the kidneys (30). Patients with GFRs above 50 ml/min were found to require daily doses of 8 mg to maintain blood glucose levels within the target values, limiting the risk for hypoglycemia. The

maximum glimepiride dose for patients with GFRs between 20 and 50 ml/min is 2-4 mg (50% of the dose when compared with that for patients with GFRs greater than 50 ml/min). Patients with GFRs less than 20 ml/min require a dosage of only 1 mg/day (31). According to the KDOQI's recommendations, glimepiride can be used with caution and at a low dose (1 mg/day) in patients with CKD stages 3 to 5. However, it is contraindicated in patients undergoing dialysis (29).

Gliclazide is a rapidly absorbed SFU with good oral bioavailability and an average half-life of 6-15 hours. It is completely metabolized, and its metabolites do not have hypoglycemic effects. The metabolites are almost completely excreted through the kidneys. According to the KDOQI's recommendations, gliclazide is considered safe in all stages of renal failure (29).

Insulinotropic meglitinide analogues

Meglitinides are insulin secretagogue agents that differ from SFUs because they have glucose-dependent insulinotropic activity, and they are therefore associated with a lower hypoglycemia risk. However, meglitinides are responsible for replacing insulin secretion in the early postprandial period (32). Unlike the target of classical SFUs, repaglinide acts on the SFU receptor associated with an ATP-dependent potassium channel. It is metabolized in the liver by the cytochrome P450 isoform CYP3A4; therefore, there is a high probability of enzyme interaction. Repaglinide is considered safe in mild to moderate renal failure. There is conflicting information regarding its safety profile in CKD stages 4-5. Repaglinide is not recommended for patients over 75 years of age with mild to moderate CKD.

Nateglinide is rapidly and completely absorbed after oral administration, and its peak plasma concentration is achieved within 1 hours postdose, with an average half-life of 1.8 hours. It is metabolized in the liver by cytochrome P450 isoenzymes CYP2C9 and CYP3A4, and 10% of the intact drug is excreted by the kidney. No drug interactions have been recorded. Nateglinide is contraindicated for patients with advanced stages of CKD (29).

Biguanide

Metformin is the only commercially available biguanide. Acting only in the presence of insulin, it promotes decreased hepatic glucose production by reducing hepatic gluconeogenesis. As an insulin sensitizing agent, it optimizes glucose uptake by peripheral tissues in the presence of insulin (muscle and liver); it also has lipolytic

activity. Metformin is rapidly absorbed in the small intestine, and it reaches its maximum concentration approximately 2 hours after oral administration. It does not bind to plasma proteins and is not metabolized, and it is rapidly excreted through the kidneys (33).

The most worrisome adverse effect is lactic acidosis, which occurs rarely. In a series of 11,800 patients who were treated for an average period of 2 years, the incidence of lactic acidosis was 9 cases per 100,000 treated patients (34). By comparison, there were approximately 40-64 cases of lactic acidosis per 100,000 patients treated with phenformin (which was withdrawn from the market). There are known predisposing conditions or true contraindications to its use due to the risk of precipitating a potentially fatal lactic acidosis. According to the recommendations of the UK National Institute for Health and Clinical Excellence (NICE) (2009) the metformin dose should be decreased in chronic kidney disease with eGFR <45 ml/min and should be discontinued when the eGFR falls below 30 ml/min/1.73 m² (35). Following the recommendations of the US Food and Drug Administration (FDA), metformin is contraindicated when serum creatinine is ≥ 1.5 mg/dl for males or ≥ 1.4 mg/dl for females (36). It is also contraindicated for additional conditions such as liver failure, alcohol abuse, heart failure, prior history of lactic acidosis, conditions of decreased renal perfusion and hemodynamic instability due to infection or other causes (33). The reality of severe metformin-induced lactic acidosis in the absence of chronic renal impairment raises the question of limiting its use in these patients (37).

Thiazolidinediones

Thiazolidinediones belong to the group of insulin-sensitizing agents that act peripherally on muscle, fat and liver tissues. They promote glucose utilization and decrease glucose production. Thiazolidinediones act by stimulating a specific nuclear receptor: the peroxisome proliferator-activated receptor (PPAR).

Some evidence exists regarding the benefits of thiazolidinediones in the various components of metabolic syndrome and its renoprotective effect (38). Pioglitazone and rosiglitazone are currently commercially available.

Rosiglitazone has been associated with the precipitation of episodes of heart failure; therefore, it is not recommended by the ADA (2012) (10). The RECORD study found that rosiglitazone is associated with an increased risk of heart failure and fractures, which occur primarily in females. An association with acute coronary syndrome is questionable (39).

Another adverse effect associated with the use of this pharmacological class (particularly rosiglitazone) is the worsening

of osteopenia/osteoporosis and the consequent increased fracture risk. Fluid retention is another important adverse effect of this pharmacological class; it especially occurs when the drug is combined with insulin. Precipitation of the onset of peripheral edema occurs globally in 4%-6% of patients and is more common in patients with heart failure.

Thiazolidinediones are considered safe for all stages of CKD, but they are rarely used due to the risk of fluid retention and the precipitation of acute pulmonary edema associated with heart failure.

Manley et al conducted a retrospective study of the safety profile and efficacy of thiazolidinediones in a population of patients undergoing hemodialysis. The primary differences between pioglitazone and rosiglitazone involved interdialytic weight gain, which was particularly associated with rosiglitazone. The use of the pharmacological group of thiazolidinediones is otherwise considered safe and effective in the population of patients undergoing hemodialysis (40).

Alpha-glucosidase inhibitors

Three drugs – miglitol, acarbose and voglibose – reversibly inhibit the intestinal α -glucosidase enzyme.

Acarbose is considered to be minimally absorbed, although some evidence suggests that approximately 35% of the dose can be absorbed in the form of metabolites.

The KDOQI's recommendations are that acarbose is contraindicated in CKD stages 3-5 due to its association with high liver toxicity (29).

Glucagon-like peptide-1 and dipeptidyl-peptidase IV inhibitors

The first incretin to be identified was glucose-dependent insulinotropic polypeptide (GIP), which is produced in the proximal small intestine. Glucagon-like peptide-1 (GLP-1) was the second hormone identified; it is produced by enteroendocrine L cells in the distal ileum and colon.

A combination of neural and endocrine stimuli conditions a rapid stimulation of GLP-1 secretion well before ingested food reaches the distal ileum and colon.

GLP-1 receptor agonists and dipeptidyl-peptidase IV (DPP-IV) inhibitors are pharmacological classes that share similar glucoregulatory characteristics. They exhibit a glucose-dependent insulinotropic activity and an inhibitory action on inappropriately elevated glucagon secretion, without ever limiting the counter-regulatory response in hypoglycemia. GLP-1 receptor agonists promote slowed gastric emptying and induce satiety. The most frequently documented

SELECTING ANTIHYPERGLYCEMIC THERAPY IN DIABETES PATIENTS WITH CKD					
PHARMACOLOGICAL CLASS	DRUG	MILD CKD eGFR 50-80 ml/min/1.73 m ²	MODERATE CKD eGFR 30-50 ml/min/1.73 m ²	SEVERE CKD eGFR < 30 ml/min/1.73 m ²	End Stage Kidney Disease/Dialysis
SFU	Glipizide		NO DOSE ADJUSTMENT NECESSARY		
SFU	Glimepiride	2mg/day	1 mg/day	1 mg/day	NOT RECOMMENDED
Meglitinides	Nateglinide	60 mg/day	50 mg/day	NOT RECOMMENDED	NOT RECOMMENDED
DPP-IV	Linagliptin	NO DOSE ADJUSTMENT NECESSARY			
DPP-IV	Sitagliptin	100 mg/day	50 mg/day	25 mg/day	NOT RECOMMENDED
DPP-IV	Saxagliptin	5 mg/day	2.5 mg/day	2.5 mg/day	NOT RECOMMENDED
DPP-IV	Vildagliptin	10 mg/day	NOT RECOMMENDED	NOT RECOMMENDED	NOT RECOMMENDED
THIAZOLIDINEDIONE	Pioglitazone	NO DOSE ADJUSTMENT NECESSARY (pioglitazone is not licensed in the US; rosiglitazone may be a substitute)			
ALPHA-GLUCOSIDASE INHIBITORS	Acarbose	NO DOSE ADJUSTMENT NECESSARY	DOSE REDUCTION FOR eGFR < 45 ml/min/1.73 m ²		NOT RECOMMENDED
BIGUANIDES	Metformin	NO DOSE ADJUSTMENT NECESSARY	DOSE REDUCTION FOR eGFR < 45 ml/min/1.73 m ² (NICE recommendation)		NOT RECOMMENDED

Fig. 1 - Antihyperglycemic therapy in chronic kidney disease (CKD). DPP-IV = dipeptidyl-peptidase IV; eGFR = estimated glomerular filtration rate; SFU = sulfonyleurea.

adverse effects are nausea and anorexia, which are dose-dependent and tend to disappear with prolonged treatment. It is noteworthy that the weight loss that is associated with this pharmacological class is independent of anorexia; it is likely caused by induced satiety (41).

Currently, the commercially available GLP-1 receptor agonist is exenatide. It was approved by the FDA in 2006, and it is a synthetic form of a protein from the saliva of the Gila monster lizard that mimics the action of GLP-1. Exenatide is a GLP-1 analogue that is resistant to inactivation by DPP-IV; it shares 50% amino acid similarity with GLP-1, and reaches its maximum plasma concentration approximately 2 hours after administration. The half-life of exenatide is 2.4 hours, and its duration of action is 6-8 hours. It is eliminated through glomerular filtration (42). Its use is not recommended in patients with severe renal failure (i.e., GFR <30 ml/min) due to its poor tolerance and prolonged half-life (5.98 hours); it confers an increased risk of toxicity (43).

The first DPP-IV inhibitor was sitagliptin, which was approved by the FDA in October 2006. It consists of an orally administered, rapidly absorbed drug, with an elimination half-life of 8 hours, low plasma protein binding (38%), and it is not extensively metabolized by the liver (CYP3A4 and 2C8). Approximately 87% of the drug is eliminated through the kidneys (roughly 79% as intact drug and 16% in the form of metabolites), and 13% is eliminated through the intestines. The recommended dosage for individuals without renal failure is 100 mg/day. No dose adjustment is required for GFR ≥50 ml/min, whereas the dosage should be reduced to 50 mg/day for GFR ≥30 and <50 ml/min, and it should be reduced to 25 mg/day for GFR <30 ml/min or in patients undergoing hemodialysis or peritoneal dialysis (44). Saxagliptin and vildagliptin were approved later; they were already commercialised, and pharmacokinetic studies had shown their safety in mild CKD with dose reduction (45). Saxagliptin is not recommended for patients with end-stage renal disease requiring dialysis and no dose adjustment is required for estimated glomerular filtration

rate (eGFR) ≥50 ml/min/1,73 m² and in patients with eGFR between 5 to 49 ml/min/1,73 m² the dose of saxagliptin should be reduced to 2.5 mg daily (Bristol Myers Squibb-AstraZeneca 2011) (46). Vildagliptin is 85% renally excreted and is not licensed in patients with creatinine clearance less than 50 ml/min (Novartis 2011) (47). Linagliptin provides an additional therapeutic option for patients with type 2 diabetes mellitus, and in contrast to other agents in the DPP-IV class, it can be used without dose adjustment in patients with any degree of declining renal function (48, 49).

CONCLUSION

CKD is associated with insulin resistance and simultaneously with a condition of decreased insulin degradation in end-stage renal disease, which has therapeutic implications regarding the need for a reduction of insulin dosage to prevent hypoglycemia events. Based on the discussion of insulin therapy above, preference should be given to fast- and long-acting insulin analogues due to the stability of their pharmacokinetic and pharmacodynamic profiles in the different stages of CKD; however, it is necessary to adjust the dosage as renal failure progresses. Because no rules exist in insulin therapy, this must be individualized.

Because in CKD the renal elimination of drugs and their metabolites is compromised, some oral antidiabetic agents with preferential renal excretion should be used with caution because they are associated with the precipitation of hypoglycemia, which is to be feared even with the safest agents, such as glipizide and gliclazide. Especially when paired with insulin, pioglitazone has an attractive safety profile in all stages of chronic renal failure, with the exception of the risk of fluid retention. Exenatide should not be used in stages 4 and 5 of CKD, and the dose of sitagliptin and saxagliptin should be adjusted for a GFR below 50 ml/min, vildagliptin is not recommended if eGFR is below 50 ml/min/1.73 m² (Fig. 1). Metformin is contraindicated in renal failure with GFR <30 ml/min or

serum creatinine ≥ 1.5 mg/dL for males or ≥ 1.4 mg/dL for females. Patient selection for the use of metformin should be judicious beyond the contraindicated conditions. The emergence of a precipitating event that generates hemodynamic instability may pose a risk for the development of lactic acidosis associated with metformin in any patient. The oldest remaining classes of oral antidiabetic agents should not be used in CKD stages 3-5. Among the oral antidiabetic agents, glipizide and linagliptin are considered safe at any stage of CKD.

The desired level of HbA_{1c} has not been defined for this population; however, the levels should be approximately 6%-7% for type 1 diabetic patients and approximately 7%-8% for type 2 diabetes.

We raise the following question: Is insulin therapy the only option for treating type 2 diabetes mellitus in patients

with advanced-stage chronic renal failure and/or undergoing hemodialysis? From what has been shown, the answer is clearly no; however, if one is seeking the safest option for glycemic control, the answer is the use of insulin alone.

Financial support: This review had no financial support.

Conflict of interest statement: None declared.

Address for correspondence:
 Dr. Patrícia Neto
 Serviço de Nefrologia
 Hospitais da Universidade de Coimbra
 Praceta Professor Mota Pinto
 PT-3000-075 Coimbra, Portugal
 patriciaaires3@sapo.pt

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Accepted: November 9, 2012