ABSTRACT

Diabetes is an increasingly common disease with an important negative impact on patient’s morbidity and mortality, being the main cause of end stage renal disease. Management of the diabetic patient with chronic kidney disease poses additional challenges, namely with respect to defining glycaemic targets and in the therapeutics employed to achieve them. The authors review the state of the art evidence about the use of antihyperglycaemic agents in type 2 diabetes, from the perspective of a chronic kidney disease patient’s health care provider.

Keywords: Chronic kidney disease; diabetes; hypoglycaemic agents

RESUMO

A diabetes é uma patologia com uma prevalência crescente, que condiciona um importante impacto negativo na morbilidade e mortalidade dos doentes, sendo a principal causa de doença renal crónica terminal. O tratamento da diabetes no doente com doença renal crónica implica desafios adicionais nomeadamente em relação à definição dos alvos glicémicos e da terapêutica utilizada para os atingir. Os autores fazem uma revisão sobre o estado da arte da utilização dos agentes hipoglicemiantes na diabetes tipo 2 na perspectiva do profissional de saúde responsável por doentes com doença renal crónica.

Palavras-chave: Agentes hipoglicemiantes; diabetes; doença renal crónica
INTRODUCTION

Diabetes is a global public health problem and epidemiologists estimate an increase in world prevalence from 6.4% to 7.7% in the next 20 years, accounted particularly by developing countries. In Portugal, the prevalence of diabetes was estimated at 11.7%, being more frequent in men (14.2%) than women (9.5%) and increasing with age.

Diabetes has an important negative impact in morbidity and mortality, remaining a leading cause of cardiovascular disorders, blindness, amputations, and hospitalizations. Data suggest that the risk of nephropathy is currently equivalent in the two types of diabetes, affecting approximately one third of diabetics and being the most common cause of end-stage renal disease (ESRD) worldwide.

The treatment approach to diabetes should be multidisciplinary, implying lifestyle modifications, control of body weight, blood pressure, dyslipidaemia, associated comorbidities and, of course, glycaemic blood values. It poses an increasing economic burden in an increasingly economically fragile society, and optimization of resources is mandatory.

Chronic kidney disease (CKD) patients, for reasons that will be detailed below, have contraindications to many of the currently available oral antihyperglycaemic agents, making glycaemic control even more challenging. Knowledge of these absolute and relative contraindications allows us to make a more rational use of the available drugs, achieving the most favourable risk/benefit profile and, concomitantly, better clinical outcomes.

In this paper, we will review the optimal glycaemic targets for the CKD type 2 diabetic patient and discuss the therapeutics currently available to achieve them.

WHAT IS THE GLYCAEMIC GOAL IN CKD PATIENTS?

Two primary techniques are available to assess the effectiveness of the management plan on glycaemic control: self-monitoring of blood glucose and haemoglobin A1c.

Evidence that achieving an haemoglobin A1c (HbA1c) level of 7.0% is able to prevent the microvascular complications of types 1 and 2 diabetes in the general population, has long been evident from studies, such as the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS). Three recent studies (ADVANCE, ACCORD, VADT) have revealed that even more intensive glycaemic control (HbA1c 6.5%) further reduces the development of elevated albuminuria in patients with type 2 diabetes, although none showed significant benefits on creatinine-based estimates of glomerular filtration rate (eGFR).

Less is known about appropriate glycaemic control in patients with diabetes and more advanced CKD, because no prospective, randomized clinical trials evaluating the level of glycaemic control on health outcomes have been carried out in patients with CKD stages 3-5. Nevertheless, several observational studies showed that higher levels of haemoglobin A1c were associated with higher death rates in patients with diabetes and chronic kidney disease after adjusting for markers of inflammation and malnutrition. Therefore, although there is need for a much better understanding of the CKD-related characteristics of diabetes mellitus, glycaemic control can still be argued to be beneficial in preventing complications, even in dialysis-dependent patients.

However, another important factor to be taken into account is the inaccuracy of the HbA1c measurement in reflecting serum glucose concentrations in this population. Studies have shown that glucose levels in CKD patients are higher than expected for given HbA1c levels, and this is most marked in those on dialysis. Factors that may contribute to falsely decreased values of HbA1c include a reduced red blood cell lifespan, transfusions, and haemolysis. On the other hand, falsely increased values may occur, less commonly, due to carbamylation of the haemoglobin and acidosis.

Therefore, when targeting for the ideal HbA1c in our CKD patients (mainly those on stages 4 and 5), we should bear in mind that a result of 6.5% may be equivalent to a higher value. However, care not to “overtreat” hyperglycaemia is particularly important in a population at increased risk of hypoglycaemia: they have a decreased clearance of insulin and of most oral agents used to treat diabetes; renal
gluconeogenesis is impaired with reduced kidney mass; and many advanced CKD patients are frail, malnourished, non-ambulatory and may be less able to respond appropriately to hypoglycaemia\textsuperscript{17}.

Although alternatives to HbA1c have been searched (i.e., glycated albumin, which reflects glycaemic control over a shorter period\textsuperscript{16}), it still remains the best clinical marker of long-term glycaemic control despite its limitations, particularly if combined with self-monitoring of blood glucose.

In light of this knowledge, the last update of KDOQI recommendations (2012) first introduced the notion of individualized HbA1c targets. They recommended: 1) a target HbA1c of 7.0\% to prevent or delay progression of the microvascular complications of diabetes; 2) not treating to an HbA1c target of < 7.0\% in patients at risk of hypoglycaemia (advanced CKD patients were considered to be included in this group); 3) target HbA1c be extended above 7.0\% in individuals with co-morbidities or limited life expectancy and risk of hypoglycaemia\textsuperscript{16}.

**WHAT IS THE BEST THERAPEUTIC APPROACH?**

Metformin has long been recommended as the initial pharmacological therapy for type 2 diabetes, in the absence of specific contraindications, along with lifestyle interventions. This position has not been changed in the last guidelines\textsuperscript{16}. However, the consensus algorithm for the initiation and adjustment of therapy proposed by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes published in 2012 was less prescriptive than prior algorithms with respect to second line therapies. The limited data on this issue was acknowledged and combination therapy with additional oral or injectable agents was considered reasonable, with the specific choice based on an integrated approach to the patient (medical, social and economical factors)\textsuperscript{18}. Insulin is still frequently used, due to the progressive \(\beta\)-cell dysfunction that characterizes type 2 diabetes\textsuperscript{18}.

Diabetic patients with chronic kidney disease (CKD) have more limited therapeutic options. The most important reason is because a reduced GFR may lead to the accumulation of renally excreted drugs and/or their metabolites and this can induce severe side effects. Moreover, uraemia differentially affects absorption and metabolic pathways in the gastrointestinal tract and liver and, therefore, can change the systemic bioavailability of drugs in a not always predictable way. The hypoalbuminaemia commonly seen in CKD patients may also interfere with protein binding-drugs total clearance and half-life\textsuperscript{19}.

For these reasons, insulin therapy was previously commonly seen as the (only?) agent of choice to achieve glycaemic control in patients with CKD. However, and albeit the persistent lack of evidence in this field, several agents, including some of the most recent drugs available, were found to be effective and safe even in patients on dialysis and may be useful therapeutic options in this population.

In the next section, we will review the available hypoglycaemic agents from the perspective of a type 2 diabetic CKD patient’s health care provider. Table I and figure 1 provide a practical summary of the mechanism of action, advantages, adverse effects and use in renal failure of antihyperglycaemic agents, discriminating those currently commercially available in Portugal.

**BIGUANIDES**

Nowadays, metformin is the only commercially available biguanide used in the treatment of diabetes, having been first introduced in the UK in 1957. It acts by improving insulin sensitivity what, consequently, decreases hepatic gluconeogenesis and enhances peripheral glucose uptake. Importantly, it does not increase the risk of hypoglycaemia\textsuperscript{20}.

Metformin is recommended as the first line therapy for diabetes by the international consensus guidelines due to its efficacy combined with a favourable side effect profile and low cost\textsuperscript{3, 16}. The UK Prospective Diabetes Study first revealed its superiority by showing a lower mortality from cardiovascular disease in overweight patients with diabetes treated with metformin rather than sulphonylureas or insulin\textsuperscript{7}. Metformin is mainly associated with
minor gastrointestinal symptoms (anorexia, nausea, vomiting, diarrhoea and abdominal pain) and it may impair absorption of vitamin B12 and folic acid. However, it is the perceived risk of lactic acidosis in the presence of renal, hepatic, respiratory, or cardiac failure that remains one of the most important causes of caution when selecting antihyperglycaemic agents.

### Table 1

<table>
<thead>
<tr>
<th>Agent (mechanism)</th>
<th>Advantages</th>
<th>Adverse effects</th>
<th>CKD stage 3</th>
<th>CKD stage 4-5d</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biguanides</strong> (improve insulin sensitivity)</td>
<td>- No weight gain</td>
<td>- Gastrointestinal side effects</td>
<td>- Caution</td>
<td>- Avoid</td>
</tr>
<tr>
<td>- Metformin</td>
<td>- No hypoglycaemia</td>
<td>- Lactic acidosis</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Reduction in cardiovascular events and mortality</td>
<td>- VitB12 deficiency</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td><strong>Sulfonylureas – 2nd generation</strong> (increase insulin secretion by pancreatic beta cells)</td>
<td>- Well tolerated</td>
<td>- Hypoglycaemia risk</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>- Glibenclamide</td>
<td>- Reduction in cardiovascular events and mortality</td>
<td>- Weight gain</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>- Glipizide</td>
<td>- May blunt myocardial ischaemic preconditioning</td>
<td>- May blunt myocardial ischaemic preconditioning</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>- Glimepiride</td>
<td>- Effectiveness decreases over time</td>
<td>- Frequent dosing schedule</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td><strong>Meglitinides</strong> (increase insulin secretion by pancreatic beta cells)</td>
<td>- Decreases post-prandial hyperglycaemia</td>
<td>- Hypoglycaemia risk</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>- Repaglinide*</td>
<td>- Weight gain</td>
<td>- Weight gain</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>- Nateglinide</td>
<td>- May blunt myocardial ischaemic preconditioning</td>
<td>- May blunt myocardial ischaemic preconditioning</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>- Mitiglinide*</td>
<td>- Frequent dosing schedule</td>
<td>- Frequent dosing schedule</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td><strong>Alpha-Glucosidase inhibitors</strong> (slows intestinal carbohydrate digestion and consequent absorption)</td>
<td>- Nonsystemic medication</td>
<td>- Gastrointestinal side effects</td>
<td>- No dose adjustment necessary</td>
<td>- No dose adjustment necessary</td>
</tr>
<tr>
<td>- Acarbose</td>
<td>- Reduces postprandial glycaemia</td>
<td>- Dosing frequency</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>- Miglitol*</td>
<td>- Weight gain</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Voglibose*</td>
<td>- May blunt myocardial ischaemic preconditioning</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Thiazolidinediones</strong> (improve insulin sensitivity)</td>
<td>- No hypoglycaemia</td>
<td>- Weight gain</td>
<td>- No dose adjustment necessary</td>
<td>- No dose adjustment necessary</td>
</tr>
<tr>
<td>- Pioglitazone</td>
<td>- Pioglitazone also ↓ HDL cholesterol and ↓ Triglycerides</td>
<td>- Oedema</td>
<td>- No dose adjustment necessary</td>
<td>- No dose adjustment necessary</td>
</tr>
<tr>
<td>- Rosiglitazone*+</td>
<td>- Weight gain</td>
<td>- Heart failure</td>
<td>- Bone fractures</td>
<td></td>
</tr>
<tr>
<td><strong>DPP-4 inhibitors</strong> (incretin enhancers)</td>
<td>- No hypoglycaemia</td>
<td>- May cause urticaria/ angioedema</td>
<td>- No dose adjustment necessary</td>
<td>- No dose adjustment necessary</td>
</tr>
<tr>
<td>- Sitagliptin</td>
<td>- No effect on weight</td>
<td>- Cases of pancreatitis observed</td>
<td>- Sitagliptin2: 50mg/d</td>
<td>- Sitagliptin: 25mg/d</td>
</tr>
<tr>
<td>- Vildagliptin</td>
<td>-</td>
<td>- Cases of pancreatitis observed</td>
<td>- Vildagliptin2: 50mg/d</td>
<td>- Vildagliptin: 50mg/d</td>
</tr>
<tr>
<td>- Saxagliptin</td>
<td>-</td>
<td>- Long-term safety unknown</td>
<td>- Saxagliptin2: 2.5mg/d</td>
<td>- Saxagliptin: 2.5mg/d</td>
</tr>
<tr>
<td>- Linagliptin</td>
<td>-</td>
<td></td>
<td>- Linagliptin: no dose adjustment necessary</td>
<td>- Linagliptin: no dose adjustment necessary</td>
</tr>
<tr>
<td><strong>Incretin Mimetics</strong> (GLP-1 receptor agonists)</td>
<td>- Weight reduction</td>
<td>- Gastrointestinal side effects</td>
<td>- Exenatide: dose reduction2,3</td>
<td>- Exenatide: avoid</td>
</tr>
<tr>
<td>- Exenatide*</td>
<td>- Potential for improved b-cell mass/function</td>
<td>- Cases of acute pancreatitis observed</td>
<td>- Liraglutide: avoid (insufficient safety data)</td>
<td>- Liraglutide: avoid (insufficient safety data)</td>
</tr>
<tr>
<td>- Liraglutide*</td>
<td>-</td>
<td>- C-cell hyperplasia/ medullary thyroid tumours in animals</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td><strong>Insulin</strong> (increases glucose uptake by the liver and peripheral tissues)</td>
<td>- Universally effective</td>
<td>- Hypoglycaemia risk</td>
<td>- No advised dose adjustment (adjust dose based on patient response)</td>
<td>- No advised dose adjustment (adjust dose based on patient response)</td>
</tr>
<tr>
<td>- Rapid-acting, long-acting, premixed</td>
<td>- Unlimited efficacy, in theory</td>
<td>- Weight gain</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Decreases microvascular risk</td>
<td>- Injectable</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

*Not commercially available in Portugal. Data from www.infarm.pt updated in April 2013. †Contraindicated due to increased myocardial infarction risk; 1 no data available about the maximum recommended dose; 2 no dose adjustment necessary if eGFR 15ml/min/1.73m²; 3 no data available about the percentage of dose reduction.

CKD stage 3: eGFR 30-59ml/min/1.73m²; CKD stage 4: eGFR 15-29ml/min/1.73m²; CKD stage 5: eGFR <15ml/min/1.73m²; CKD stage 5d: on dialysis.
Metformin associated lactic acidosis (MALA) is defined as the presence of lactic acidosis associated with a lactate > 5mmol/l in a patient medicated with metformin. Most of the evidence for the association between biguanides and lactic acidosis is historical data from phenformin. Phenformin was in fact withdrawn from the market because of an association with fatal lactic acidosis, which was calculated to be 10-20 times greater than for metformin. The physiopathology of MALA is complex and mostly unclear. Metformin has been proposed to increase lactate production through an intracellular shift to anaerobic metabolism and impair lactate clearance by the liver. This would become particularly relevant in cases of accumulation of metformin (i.e., in renal insufficiency, as the drug main route of elimination is renal tubular secretion) or increased lactate production (i.e., inadequate tissue delivery of oxygen or excessive tissue oxygen demand). There are many published case reports that describe an association between metformin and lactic acidosis. However, they have been highly criticised because it remains difficult to establish the exclusive role of metformin as the cause of lactic acidosis, as most patients were admitted with other causes of increased lactate, such as sepsis, dehydration or cardiac heart failure. Moreover, the lack of a relation between lactic acid/metformin concentrations and mortality and the absence of an association between metformin concentration and lactic acid concentration (that was proved to exist in the case of phenformin) made some investigators suggest that the association between lactic acidosis and metformin is coincidental.

A Cochrane review of 206 comparative trials and cohort studies in patients with type 2 diabetes who were treated with metformin, found no evidence of increased risk of developing fatal or non-fatal lactic acidosis in the subgroup of metformin treated patients. However, these studies did not include patients who had contraindications for the use of metformin and so nothing could be concluded about the risk of MALA in this subpopulation. Nevertheless, there are clinical studies that corroborate the association of metformin with higher lactate levels. A Chinese study describes the result of a cross sectional measurement of lactate in 1024 diabetics in an outpatient clinic that had normal renal function and no increased risk of elevated lactate (i.e., excluded patients with chronic liver disease and cardiac insufficiency). They showed that patients medicated with metformin had a slightly but significant higher level of lactate than patients who were not on this medication. Another retrospective French study compared patients admitted to an intensive care unit for MALA who had an intentional versus accidental intoxication with metformin. They showed that metformin can, in fact, lead to lactic acidosis, although mortality was primarily associated with underlying health status and organ dysfunction.

In conclusion, causality between metformin and lactic acidosis cannot be ruled out, although its real impact in the prognosis and morbidity/mortality of diabetic patients is difficult to account for. The challenge is to differentiate who would benefit from being denied the first line medication for diabetes. The European, American, Canadian and many other national guidelines agree to contraindicate metformin in patients with CKD class 4 or higher and most suggest a cautious use in CKD class 3. While there are no randomized controlled trials (RCTs) that evaluate the safety and potential benefit of this medication, all patients should be educated to contact a health care provider and hold metformin (as well as angiotensin-converting enzyme inhibitor, angiotensin II receptor blockers, diuretics, and non-steroidal anti-inflammatory drugs), if diarrhoea or...
vomiting together with inability to tolerate oral liquids intake develops24.

■ SULFONYLUREAS

Sulfonylureas reduce blood glucose by stimulating the pancreatic beta cells to increase insulin secretion34. Therefore, their effectiveness tends to decline over time, as there is a reduction in the number of viable pancreatic beta cells35. The major risk associated with its use is hypoglycaemia19.

The first-generation sulfonylureas (acetohexamide, chlorpropamide, tolazamide and tolbutamide), the oldest oral hypoglycaemic agents, are almost exclusively excreted by the kidney and are, therefore, contraindicated in CKD due to the risk of hypoglycaemia16.

Second-generation agents (gliclazide, glimepiride, glipizide and glibenclamide) are metabolized in the liver, but some of the drugs (glimepiride and glibenclamide) excrete their active metabolites in the urine and, therefore, should be avoided in renal failure. Glipizide and gliclazide are the preferred agents and do not need dose adjustment16, 19. They are primarily metabolized in the liver and although more than 60% of their metabolites are excreted in the urine, these have no hypoglycaemic activity19.

■ MEGLITINIDES

Meglitinides are insulin secretagogues that stimulate pancreatic beta cells. Compared with sulfonylureas they are shorter-acting, have modest glycaemic efficacy and a relatively low risk of hypoglycaemia18.

There are three meglitidines (nateglinide, repaglinide, and mitiglinide) currently in clinical use but only nateglinide is available in Portugal19. Although hypoglycaemia has not been demonstrated to increase substantially with progressive falls in GFR, renal dose adjustment is recommended as drug accumulation (repaglinide) or of their active metabolites (nateglinide and mitiglinide) can occur in renal failure36-38. Accumulation of active metabolites is particularly notorious with nateglinide, that should therefore be avoided in ESRD19.

■ ALPHA-GLUCOSIDASE INHIBITORS

The antihyperglycaemic action of alpha-glucosidase inhibitors (acarbose, miglitol and voglibose) results from the reversible inhibition of membrane-bound intestinal alpha-glucoside hydrolase enzymes. Alpha-glucosidase inhibitors decrease the rate of breakdown of complex carbohydrates so that less glucose is absorbed and postprandial hyperglycaemia is lowered19.

Acarbose is metabolized exclusively within the gastrointestinal tract and approximately a third of these metabolites are absorbed and subsequently excreted in the urine, one of them with alpha-glucosidase inhibitory activity. Although normally less than 2% of the total administered dose is excreted in the urine as active drug, patients with severe renal impairment (creatinine clearance < 25 mL/min) can attain peak plasma concentration of acarbose about 5-fold higher39.

Miglitol is absorbed without metabolism and is eliminated by renal excretion as unchanged drug40. As these drugs act locally, dose adjustment to correct for the increased plasma concentrations is not feasible19. Although important adverse side effects have not been described, data are scarce and its generalized use in advanced renal failure is not recommended16, 41.

■ THIAZOLIDINEDIONE

Thiazolidinediones (TZDs) are peroxisome proliferator–activated receptor gamma (PPARγ) agonists that improve insulin sensitivity in skeletal muscle and reduce hepatic glucose production42. They do not increase the risk of hypoglycaemia and may be more durable in their effectiveness than sulfonylureas and metformin18.

There are currently two available agents from this class: pioglitazone and rosiglitazone. Pioglitazone, which seems to also act like a partial PPARα agonist, appears to decrease triglycerides, increase HDL cholesterol and have a modest benefit on cardiovascular events42, 43. Rosiglitazone, an apparently pure PPARγ agonist, is no longer widely available
owing to concerns of increased myocardial infarction risk.44,45.

Drugs in this class do not need renal dose adjustment because they have predominant hepatic metabolism and their pharmacokinetic profile is independent of renal function.46, 47. However, because their side effect profile includes weight gain, fluid retention that may lead to oedema and/or heart failure, and increased risk of bone fractures, they should be used with caution in the chronic kidney disease population.3, 16, 18. Moreover, pioglitazone has been associated with a possible increased risk of bladder cancer.48.

### DPP-4 Inhibitors

The oral dipeptidyl peptidase 4 (DPP-4) inhibitors decrease the breakdown of the incretin hormones, such as glucagon-like peptide 1 (GLP-1). GLP-1 is an intestinal hormone with a meal-induced secretion that stimulates insulin secretion and suppresses glucagon release in a glucose-dependent manner.49.

They are generally well tolerated, weight neutral and do not cause hypoglycaemia.3, 18. All can be used in CKD patients, but sitagliptin, saxagliptin, and vildagliptin need dose adjustments, as opposed to linagliptin that can be used in the normal doses.16.

### Incretin Mimetics

Incretin mimetics (exenatide and liraglutide) are subcutaneously injectable GLP-1 receptor agonists that thereby stimulate pancreatic insulin secretion and suppress pancreatic glucagon output in a glucose dependent manner, slow gastric emptying, and decrease appetite.19. Their main advantage is weight loss.18. Exetanide has a renal excretion and should be avoided in patients with eGFR < 30ml/min/1.73m².16. Liraglutide is not significantly eliminated by the kidneys and pharmacokinetic studies suggest blood levels are not affected by renal failure.50. However, there is still insufficient safety data to recommend its use in CKD patients.16.

### Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors

SGLT2 inhibitors are the most recent class of drugs approved by the United States Food and Drug Administration (FDA) for the treatment of diabetes, still not available in Portugal. They are currently represented by canagliflozin and improve glycaemic control in an insulin-independent fashion through inhibition of glucose reuptake in the kidney.51.

Phase III clinical trials have shown improved glycaemic control in type 2 diabetes associated with a relatively low hypoglycaemia risk and weight loss-promoting effect. The major side effects appear to be urinary and mycotic genital infections and adverse effects related to osmotic diuresis and reduced intravascular volume.51, 52. A phase III RCT with canagliflozin against placebo was performed in 272 CKD 3 patients, concluding that this new agent was generally well tolerated and might be a possible therapeutic option for this subpopulation. However, they did report a higher decrease in eGFR at 26 weeks in the canagliflozin arm compared to placebo, for which statistical significance was not performed. While data are still scarce, caution should be taken before using them in CKD patients.53.

### Other Non-Insulin Hypoglycaemic Drugs

There are many other agents that are being investigated as potential therapeutic weapons in diabetes. Bile acid sequestrants (i.e., colesevelam)54, dopamine-2 agonists (i.e., bromocriptine)55 and amylin mimetics (i.e., pramlintide)56 are some of the most promising drugs that are now defining their potential role in the treatment of diabetes.

### Insulin

Exogenous insulin is the most potent antihyperglycaemic agent, with a theoretically universal and unlimited effectiveness. However, because it is an injectable drug associated with hypoglycaemia risk...
and weight gain, it is most commonly considered a second or third line therapy\textsuperscript{18}.

Due to the progressive Beta-cell dysfunction that characterizes type 2 diabetes, insulin replacement therapy is frequently required, alone or in combination with other agents\textsuperscript{18}. This is particularly true in the renal failure population, where the therapeutic options are more limited.

There are a variety of insulin preparations, which specific indications and pharmacokinetics go beyond the scope of this review. None of them is contraindicated in CKD patients and dose should be adjusted based on patient response\textsuperscript{16}. Due to the fact that the kidneys metabolize 25\% of circulating insulin, progressive declines in eGFR are expected to increase the exogenous (and residual endogenous) blood levels and thus decrease the requirement dose of exogenous insulin\textsuperscript{41}.

\section*{SUGGESTED SCHEDULES IN THE RENAL FAILURE PATIENT}

Guidelines for the treatment of diabetes are becoming less strict and, as previously stated, should be based upon clinical, social and economical criteria\textsuperscript{18}. Having this in mind, and according to the review above, we recommend the use of the following drugs in chronic kidney disease patients in monotherapy or, if necessary, in 2 or 3 drug-combinations:

- **CKD 3**: Metformin + second generation sulphonylureas (gliclazide or glipizide)/meglitidines (any) + DPP4 inhibitors (any)/Incretin mimetics (exenatide) + Thiazolidinediones (pioglitazone) + alpha-Glucosidase inhibitors (any) + insulin.

- **CKD 4-5d**: Second generation sulphonylureas (gliclazide or glipizide)/Meglitidines (repaglifine or mitiglinide) + DPP4 inhibitors (any) + Thiazolidinediones (pioglitazone) + insulin.

The order does not mean to indicate any specific preference. However, clinicians should not forget the advantages and possible side effects of each class of drugs when prescribing. Namely, thiazolidinediones can cause fluid retention, heart failure and bone fractures and, therefore, may be contraindicated in the subgroup of renal failure patients with cardiovascular and/or mineral bone disease. Additionally, renal patients that have previously been exposed to cyclophosphamide would have a cumulative risk of bladder cancer if given rosiglitazone. Metformin should be used cautiously, as explained in the former section. When prescribing drug combinations, agents with the same mechanism of action should not be favoured (these agents are separated above by a slash).

\section*{CONCLUSION}

Diabetic patients with chronic kidney disease are a particular challenging population to treat. While glycaemic targets are still not well validated, HbA1c and daily finger-stick blood glucose measurements seem to be the most reasonable measure of glycaemic control. Metformin, the fist-line therapeutic agent in the general population, should be used with caution in CKD class 3 and is contraindicated when eGFR < 30ml/min/1.73m\textsuperscript{2}. Alternatives to be used alone or in combination, without dose adjustment, include some second generation sulphonylureas, thiazolidinediones and insulin. Nevertheless, thiazolidinediones may cause oedema and heart failure and should be used with caution in this population. Meglitinides, DPP-4 inhibitors and some incretin mimetics can also be used with dose adjustment.

In conclusion, although there are still many open questions about the ideal treatment of diabetic CKD patients, there are now many available therapeutic options, that if used with knowledge, can improve the quality and quantity of life of these patients.

\textit{Conflict of interest statement.} None declared

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\end{enumerate}


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