Diabetes and Kidney Disease: The Challenging Duo - review article

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Abstract

Title
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Summary
This review article will discuss diabetes management issues and examine the pharmacological treatment options in patients with diabetic kidney disease, with a focus on glycaemic targets, risks and benefits of the spectrum of oral and injectable hypoglycaemic agents.

This article aims to increase awareness of the advantages and disadvantages of the available treatment for diabetes to support the safe prescribing, monitoring and optimisation of therapy in this patient population.

Keywords: diabetic kidney disease, hypoglycaemic agents, glycaemic targets, insulin.

Background

Managing diabetes in patients with kidney disease is challenging because renal disease can complicate glycaemic control.

There are an estimated 4.5 million people living with diabetes in the UK.[1] Since 1996, the number of people diagnosed with diabetes in the UK has more than doubled.[1] It has been well established that diabetes is one of the most common causes of kidney disease.[2] Although the development of diabetic nephropathy is slow and usually takes at least twenty years to develop, about 3 in 4 people with diabetes will develop some stage of kidney disease during their lifetime, with nearly 1 in 5 developing overt kidney disease. However, end-stage renal disease, for which renal replacement therapy is required, appears to be decreasing in people with both types of diabetes.[1] This is most likely related to improved management, tighter glycaemic control and earlier detection in type 2 diabetes.

Glycaemic targets

The National Institute for Health and Care Excellence (NICE) recommends that clinicians should work with people with type 2 diabetes to achieve an HbA1c target of <53mmol/mol.[3]

Guideline	HbA1c target
NICE[3]	<53mmol/mol (7.0%)
ADA/EASD[4]	Around 53mmol/mol (7.0%)
International Diabetes Federation[5]	
Functionally independent	53 -59 mmol/mol (7.0-7.5%)
Functionally dependent	53-64 mmol/mol (7.0-8.0%)
Frail elderly or with dementia	<70 mmol/mol (8.5%)

Table 1: National and international recommendations on HbA1c targets for type 2 diabetes

Drug class	Advantages/benefits	Disadvantages/risks	Recommendations
Biguanide (metformin)	• Extensive experience • No hypoglycaemia • Weight neutral • Benefits in reduction in macrovascular complications	• Renally-cleared, accumulation in renal impairment, increased risk of lactic acidosis • GI side effects • Frequent dosing schedule	• eGFR 30-45: starting treatment not recommended, review existing treatment • eGFR <30: contraindicated • Withhold in acute kidney injury, sepsis, acute cardiac or respiratory failure → increased risk of lactic acidosis
Sulphonylureas	• Rapid correction of hyperglycaemia	• Hypoglycaemia is common • Weight gain • Accumulation in renal impairment for those cleared by the renal route	• If a sulphonylurea is required, avoid long-acting sulphonylurea in renal impairment
Postprandial regulators (meglitinides)	• Short-acting, flexible dosing schedule • Lower risk of hypoglycaemia compared to sulphonylurea • Repaglinide suitable in moderate renal impairment	• Frequent dosing schedule	• Nateglinide not recommended in moderate renal impairment
Pioglitazone	• No hypoglycaemia • Once daily dosing • No dose adjustment in moderate to severe renal impairment	• Weight gain • New onset/worsening of heart failure (due to water retention) • Increased bone fractures	• Not recommended in those with heart failure, osteoporosis
DPP4 inhibitors	• No hypoglycaemia • Weight neutral • Once daily dosing	• GI side effects • Pancreatitis	• Linagliptin – no dose adjustment at any stage of renal impairment • All others require dose adjustment according to renal function
SGLT2 inhibitors	• No hypoglycaemia • Weight loss • Once daily dosing	• Genitourinary infections • Dehydration/ hypotension • Risk of euglycaemic DKA	• Initiation not recommended in eGFR<60 • Close blood pressure monitoring when used with diuretics, dapagliflozin and canagliflozin not recommended in patients receiving loop diuretics • Patient counselling on recognition of signs and symptoms of dehydration and DKA • Withhold treatment during acute medical illness or in the perioperative period with presence or risk of dehydration

Table 2: Summary of the advantages and disadvantages of oral hypoglycaemic agents

However, it also emphasises the need to consider patient factors and preferences when individualising glycaemic targets, which is supported by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) in their position statement for the management of hyperglycaemia in adults with type 2 diabetes.[4]

Treatment targets recommended by national guidelines are illustrated in Table 1. Glycaemic targets for patients with renal impairment follow the recommendations for the general type 2 diabetes population. The Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines for Diabetes and Chronic Kidney Disease[6] endorsed a target HbA1c of around 53mmol/mol for this patient group.

Oral hypoglycaemic agents (OHAs) – which is the best for my patient with kidney disease?

The current spectrum of therapeutic options for managing hyperglycaemia is fascinating. However, for many, it is recommended that they be used with caution in renal impairment. Clinicians need to be mindful of the impact of chronic kidney disease (CKD) on the choice of OHA. Table 2 summarises the risks and benefits of each class of OHA and highlights the associated recommendations to promote safe use of these agents.

Metformin has extensive evidence and is the first agent of choice for patients with type 2 diabetes if tolerated. It can be used as an adjunct to insulin for people with type 1 diabetes to reduce insulin doses.[3,7] Recent updates from the FDA[8] and EMA[9] extended the use of metformin in renal impairment based on evidence confirming the relative safety of metformin in patients with moderate renal impairment. Starting metformin in patients with an eGFR between 30-45 mL/minute/1.73 m^2 is not recommended. For patients already taking metformin, the benefits and risks of continuing treatment should be assessed when eGFR falls below 45 mL/minute/1.73 m^2 and treatment should be discontinued when eGFR is below 30 mL/minute/1.73 m^2. As a result, the product information has been updated, recommending a maximum daily dose of 2,000 mg/day in CKD stage 3a (GFR = 45-59 mL/min) and 1,000 mg/day in CKD stage 3b (GFR = 30-44 mL/min).[10]

Sulphonlyureas are effective in the rapid reduction of plasma glucose level and the alleviation of osmotic symptoms, but hypoglycaemia is a well-recognised side effect.[11,12] The UKPDS[13] showed that the mean annual incidence of patients experiencing at least one hypoglycaemic episode of any intensity over a 10 year period was 11.0% with chlorpropamide, 17.7% with glibenclamide, and 36.5% with insulin. Study data collected from the Clinical Practice Research Datalink (CPRD), which contained medical records for more than 11 million patients from 674 practices in the United Kingdom, found a 2.5-fold increased risk of hypoglycaemia in patients taking sulphonylurea monotherapy compared to patients taking metformin monotherapy.[14] This higher risk of hypoglycaemic events was further increased in patients with an eGFR <30 mL/min/1.73 m^2, with a 4-fold increased risk in patients with impaired renal function taking suphonylurea monotherapy compared to patients with impaired renal function taking metformin monotherapy. The risk of hypoglycaemia was also significantly higher in patients taking a higher sulphonylurea dose (>10 mg glibenclamide or equivalent). Gliclazide, the sulphonylurea of choice in UK practice, showed a similar risk of hypoglycaemia compared with glimepiride, glipizide, and tolbutamide.[14] However, a systematic review examining the risk of hypoglycaemia when sulphonylurea is added onto metformin monotherapy identified gliclazide to be the sulphonylurea of lowest hypoglycaemia risk compared to glipizide, glimepiride, and glibenclamide.[15] It has also been observed that hypoglycaemia rates are higher in people with CKD with or without diabetes compared to those with normal renal function.[16]

Postprandial regulators, namely repaglinide and nateglinide, like sulphonylureas, stimulate insulin release by closing KATP channels on pancreatic β-cell membranes.[4] Although they are not commonly prescribed in UK practice among other OHAs, they have a place in therapy and an advantage in renal impairment. With its rapid onset and short duration of action, it has the advantage of increased dosing flexibility. To avoid hypoglycaemia, if a meal is omitted, the corresponding dose should also be omitted. Nattrass et al[17] demonstrated that treatment with repaglinide provided similar glycaemic control determined by HbA1c compared to treatment with a sulphonylurea, with an absolute risk reduction of 60% for major hypoglycaemia. Metabolism of repaglinide has been shown to be unaffected by mild to moderate renal dysfunction, due to it being extensively metabolised in the liver to inactive metabolites.[17] In contrast, the active metabolite of nateglinide is renally-cleared and nateglinide should not therefore be used in moderate renal impairment (eGFR <60 mL/minute/1.73 m^2). However, its active metabolite is cleared by haemodialysis, hence nateglinide is safe to use in patients undergoing haemodialysis.[18]

Pioglitazone has demonstrated both efficacy and safety in renal impairment for which dose adjustment is not required and rarely causes hypoglycaemia. However, its side effect of water retention can limit its use in patients with heart failure and in CKD, in particular dialysis patients.[19] It also increases the risk of bone fractures, which can also limit its use in those with increased bone loss, such as in renal osteodystrophy.[18]

The dipeptidyl-peptidase-4 (DPP4) inhibitors, inhibit the enzymatic breakdown of glucagon-like-peptide 1 (GLP-1), causing an increase in insulin secretion responsive to food intake.[20] They are all suitable for use with dose adjustment in moderate to severe renal impairment, with the exception of linagliptin, which does not require dose adjustment in any stage of renal impairment due to its excretion via the bile.[21] Lower doses of sitagliptin (25mg daily) can be used in patients on haemodialysis and peritoneal dialysis.[22] Saxagliptin is not recommended in ESRD patients requiring dialysis.[23] Vildagliptin at reduced dose should be used with caution in ESRD and haemodialysis patients due to limited clinical data.[24] Lower doses of alogliptin (6.25mg daily) can be used in dialysis; however, alogliptin has not be studied in patients on peritoneal dialysis.[25]

Sodium glucose transporter 2 (SGLT2) inhibitors are effective in improving glycaemic control and promote weight loss by reducing glucose reabsorption in the proximal renal tubules, leading to glucosuria and calorie loss.[26] They have been shown to achieve a moderate HbA1c reduction of approximately

0.66–1.03%,[27,28,29] whilst associated with a low hypoglycaemia risk and moderate weight loss of 2–3 kg.[30-33] Side effects are mainly attributed to the associated glucosuria, which include genitourinary infections, dehydration and hypotension. Efficacy is dependent on good renal function, hence they are not recommended for treatment initiation in renal impairment with eGFR <60 mL/minute/1.73 m.[2,27,28,29] Treatment with canagliflozin and empagliflozin are licensed to be used down to eGFR 45 mL/minute/1.73 m[2,28,29] but with a compromise in significant decrease in efficacy. A 24-week study showed a non-significant reduction of HbA1c of 0.41% and 0.44% with dapagliflozin 5mg and 10mg vs 0.32% with placebo in moderate impairment.[34] A 26-week trial in patients with GFR 30-50 ml/minute demonstrated an HbA1c reduction of 0.33% and 0.44% with canagliflozin 100mg and 300mg vs placebo.[35] A study using empagliflozin 25mg in 374 patients with GFR 30-60 ml/minute found an HbA1c improvement of 0.37% compared to placebo.[36]

In response to recent reports of severe and life-threatening euglycaemic diabetic ketoacidosis (euDKA) in patients treated with a SGLT2 inhibitor, an EMA[37] safety alert was published with recommendations for high-risk groups such as those with low insulin-producing capacity, a sudden reduction in insulin dose,

GLP-1 agonist	Dosing recommendation in renal impairment (eGFR in mL/min/1.73 m²)	Safety & efficacy	Risks/adverse effects
Exenatide	eGFR >50: 10mcg BD eGFR 30-50: 10mcg BD (with caution) eGFR <30: avoid	Well tolerated in mild to moderate renal impairment[46]	• Case reports of AKI, not appeared to be directly nephrotoxic, possible natriuretic effect causing dehydration[47,48,49]
Exenatide modified-release	eGFR >50: 2mg weekly eGFR <50: avoid		
Liraglutide	eGFR >30: 1.2-1.8mg OD eGFR <30: avoid	Patients with GFR 30-59 with liraglutide 1.8mg vs placebo as add-on at 26 weeks:[50,51] • HbA1c reduction (1.05% vs 0.38%), weight loss, fewer hypoglycaemic events • Tolerated with no change in renal function UK clinical practice audit[52] findings indicate liraglutide 1.2mg is safe and efficacious in mild to moderate renal impairment	Higher GI side effects in those with renal impairment[52]
Lixisenatide	eGFR >50: 20mcg OD eGFR 30-50: 20mcg OD (use with caution) eGFR <30: avoid	Well tolerated in mild and moderate renal impairment[53] No difference in HbA1c, fasting and postprandial glucose in renal impairment vs normal renal function[53,54]	Increased plasma conc. in moderate renal impairment[53] Higher side effects in those with mild renal impairment[53,54]
Dulaglutide	eGFR >30: 0.75mg or 1.5mg weekly eGFR <30: avoid	Pharmacokinetics similar in mild severe renal impairment (and dialysis) compared to normal renal function[55]	
Albiglutide	eGFR >30: 30mg or 50mg weekly eGFR <30: avoid	Increased glycaemic lowering effect in lower eGFR[56]	Higher GI side effects in severe renal imp[airment compared to mild and moderate renal impairment[56]

Table 3: Summary of safety and efficacy of GLP-1 agonists in renal impairment

during the time of increased insulin requirement (e.g. illness or surgery) or conditions that can restrict food and fluid intake. Clinicians should inform patient of the signs and symptoms of DKA and seek medical attention immediately if these symptoms arise, test for raised ketones in patients presenting with symptoms of DKA and stop treatment if DKA is suspected or diagnosed. Treatment with a SGLT2 inhibitor should be interrupted prior to major surgery or during serious medical illness related to volume depletion.[37]

Injectable therapies – GLP-1 agonists

GLP-1 receptor agonists improve HbA1c by stimulating glucose-dependent insulin release, inhibiting glucagon secretion and promote weight loss by suppressing appetite.[20] This class of agents are contraindicated in severe renal impairment (eGFR <30 mL/minute/1.73 m^2),[39-43] with exenatide modified-release contraindicated in eGFR <50 mL/minute/1.73 m^2.[44] Although use with caution is generally recommended with GLP-1 agonists in patients with moderate renal impairment,[45] there is evidence to support the safety of these agents in mild and moderate renal impairment. Table 3 summarises the evidence on the safety and efficacy of GLP-1 agonists in renal impairment.

Effects of CKD on insulin metabolism

It was found that, compared to people without CKD, the rate of hypoglycemic events was twice that for those with CKD. Moreover, hypoglycaemia affects CKD patients with and without diabetes.[16] This can be explained by the fact that CKD alters the pharmacokinetics of all insulin. Endogenous insulin is released from the pancreas into the portal system, with 40-50% undergoing first-pass metabolism in the liver and 30-80% being metabolised by the kidneys.[57] Conversely, exogenous insulin does not undergo first-pass liver metabolism, hence the kidneys are primarily responsible for exogenous insulin metabolism.[57] A study has shown when creatinine clearance reaches below 20 ml/min, renal clearance of insulin is markedly reduced.[58] CKD patients with residual diuresis of less than 500 ml/day showed a reduction in insulin needs by about 29%.[59] As a result, the risk of hypoglycaemia is increased when the insulin dose is not reduced. Other attributing factors to decreasing exogenous insulin requirements in patients with diabetic kidney disease include reduced renal gluconeogenesis and weight loss associated with uraemia-induced anorexia.[60]

CKD further complicates glycaemic control

CKD patients are more susceptible to plasma glucose fluctuations as some mechanisms in CKD can cause hyperglycaemia. Uraemia-associated insulin resistance is a recognised metabolic alteration in CKD, which begins to occur when creatinine clearance is less than 50 ml/min. Insulin sensitivity can reduce by as much as 60% in uraemic patients in predialysis state.[57] Secondary hyperparathyroidism and vitamin D deficiency reduces insulin-secreting capacity of pancreatic β cells, and medical or surgical therapy has been shown to improve glucose tolerance and insulin secretion.[57]

HbA1c may be a misleading measure of glycaemic control in patients with CKD, which is associated with a shortened red cell survival and HbA1c can be falsely low. However, other processes in CKD, such as decreased erythropoietin production, higher levels of carbamylated haemoglobin, and higher glucose exposure during dialysis, can raise the HbA1c.[61] Generally, HbA1c tends to be falsely lowered in chronic renal failure.[61,62]

What do the guidelines say about insulin therapy in CKD patients?

There are no specific national guidelines on insulin management in this patient group with recommendations on glycaemic targets and most appropriate insulin regimens, which places the emphasis on individualisation of therapy. Table 4 shows the general recommendation from the American College of Physicians on insulin dose adjustment for people with CKD.

The management of patients with diabetes and kidney disease is complex and optimising glycaemic control can be difficult due to the effects of concurrent nephropathy, in particular in those undergoing renal replacement therapy.

Glycaemic targets should be individualised and optimal glycaemic control is achievable with careful selection from the wide range of diabetes treatment options. Patients should be closely monitored for medicine-related adverse effects and disease progression.

The prevention and treatment of diabetic kidney disease and related complications requires a multidisciplinary specialist teams approach.

Declaration of interests

The author reports personal fees as Consultancy advisor for Eli Lilly UK, outside the submitted work.

Renal function	Insulin dose adjustment
eGFR >50 ml/min	No dose adjustment is required
eGFR 10–50 ml/min	Reduce dose by 25%
eGFR <10 ml/min	Reduce dose by 50%

Table 4: General principle on insulin dose adjustment in CKD[60,63]

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