Managing blood glucose levels in patients with diabetes and renal impairment

Diabetes is the most common cause of end-stage renal disease in many parts of the world (Renal Association, 2014). While the mainstay of management of diabetes in patients with renal disease is to optimize blood pressure and reduce cardiovascular risk, glycaemic management of the diabetic patient remains important. Patients with diabetes and renal impairment can have complex issues related to glucose management, including a limited range of anti-hyperglycaemic medication, glycaemic variability, increased risk of other diabetes complications, and difficulties in monitoring glucose control using standard methods. This article describes some important issues to consider when managing glucose levels in patients with diabetes and renal disease.

Diagnosing and managing renal disease in patients with diabetes

The pathogenesis of diabetic nephropathy is thought to involve a complex interplay of genetic, environmental and metabolic pathways, with podocyte loss, epithelial dysfunction, inflammation and cell hypertrophy contributing to initiation and progression of the condition (*Figure 1*) (Reidy et al, 2014).

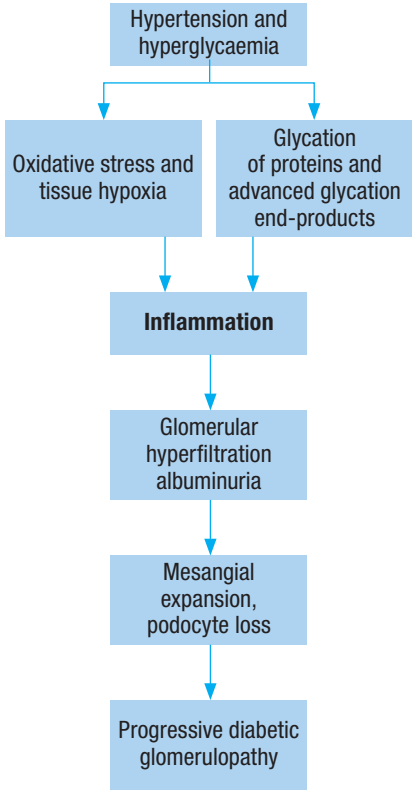
The onset of renal disease in people with diabetes heralds a dramatically increased risk of morbidity and premature mortality, particularly from cardiovascular disease (Parving and Rossing, 2015). Kidney Disease Improving Global Outcomes (KDIGO) guidelines now classify diabetic nephropathy according to both estimated glomerular filtration rate and albumin:creatinine ratio, with increasing cardiovascular risk noted in patients with poorer renal function and higher albumin excretion (*Table 1*) (Levey et al, 2011).

All patients with diabetes should have their serum creatinine level (and thereby estimated glomerular filtration rate) and albumin:creatinine ratio measured yearly, the latter ideally on a first voided urine sample. If albumin:creatinine ratio is elevated (>2.5 mg/mmol in men or >3.5 mg/mmol in women), the sample should be repeated and urinary tract infection should be excluded.

If the albumin:creatinine ratio is persistently elevated (on two or more occasions), diabetic nephropathy can be diagnosed, with microalbuminuria (albumin:creatinine ratio 2.5–30 mg/mmol) or macroalbuminuria (albumin:creatinine ratio >30 mg/mmol). Consideration should be given to non-diabetic renal disease if the patient has non-typical features, such as haematuria, rapid decline in renal function, or lack of hypertension or retinopathy, and further nephrological assessment may be necessary.

The mainstay of treatment of diabetic nephropathy is the use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers to achieve a blood pressure under 130/80 mmHg (Yamout et al, 2014). Cardiovascular risk should be minimized, with the use of statins and smoking cessation, and careful monitoring of renal function and screening for other diabetic complications is required. Once chronic kidney disease stage 3 is reached (estimated glomerular filtration rate <60 ml/min/1.73m^2), haemoglobin and calcium levels should also be monitored and treated if renal anaemia or renal bone disease develop. Referral to a nephrologist is required once estimated glomerular filtration rate reaches 30 ml/min/1.73m^2 or less (chronic kidney disease stage 4).

Figure 1. The pathogenesis of diabetic nephropathy.



Does management of hyperglycaemia matter in patients with chronic kidney disease?

Seminal studies in the last two decades have shown that improving glucose control reduces the risk of microvascular complication in patients with type 1 diabetes and type 2 diabetes (UKPDS Study Group, 1998; DCCT/EDIC Research Group, 2014). More recently, however, concerns over very tight glucose control have been raised, with data from the ACCORD study suggesting a 22% increased risk of mortality in people with very tight glycaemic control (Action to Control Cardiovascular Risk in Diabetes Study Group, 2008).

Most guidelines suggest that glucose control should be individualized, with tight glycaemic control advocated in younger

Dr Tahseen A Chowdhury is Consultant in Diabetes in the Department of Diabetes and Metabolism
Dr Sam O'Toole is Specialist Trainee in Diabetes and Endocrinology is Department of Diabetes and Metabolism
Professor M Magdi Yaqoob is Professor of Nephrology in the Department of Nephrology, Barts and the London School of Medicine and Dentistry, London E1 1BB
Correspondence to: Dr TA Chowdhury (Tahseen.Chowdhury@bartshealth.nhs.uk)

patients with shorter duration of diabetes and fewer comorbidities (Inzucchi et al, 2012; National Institute for Health and Clinical Excellence, 2015). Glycaemic control may be less tight in older patients, with longer duration of diabetes and comorbidities. Patients with diabetes and renal disease have frequently had diabetes for more than 10 years, and may have significant comorbidities, in particular vascular disease. In this circumstance, hypoglycaemia may be a significant risk and should be avoided. Therefore tight glucose control may not be desirable in patients with renal disease, and indeed as renal disease progresses, may be more difficult to achieve (see later).

There is no hard evidence that tight glycaemic control reduces the rate of decline of renal function in patients with diabetes and renal impairment. Similarly, there is a lack of evidence for tight glycaemic control in diabetic patients on renal replacement therapy. Aiming for a glycated haemoglobin (HbA_{1c}) level somewhere around 53–68 mmol/mol (7.0–8.5%) may be safer and more realistic in patients with diabetes and chronic kidney disease, especially those with chronic kidney disease stage 4 and 5.

Monitoring glucose control in patients with renal impairment

Glucose control in patients with diabetes can be assessed using self-monitoring of blood glucose, or using glycated proteins such as HbA_{1c}. Certain conditions may impact on the reliability of HbA_{1c} as a glycaemic marker, as they either interfere with the HbA_{1c} assay or affect red cell survival.

In patients with renal disease, increased levels of urea can lead to the formation of carbamylated haemoglobin, which interferes with the HbA_{1c} assay. Iron deficiency, which is common in patients with renal impairment, can lead to a falsely elevated HbA_{1c}. Furthermore, blood transfusions, iron transfusions or erythropoeitin may lead to a rapid increase in haemoglobin, and a higher proportion of younger red cells, leading to an underestimation of HbA_{1c}.

Therefore, self-monitoring of glucose levels may be necessary, and indeed intermittent continuous blood glucose monitoring using a sensor may be useful, especially in patients on dialysis. Certain peritoneal dialysis fluids interfere with glucose meters, and care should be taken to ensure that appropriate meters are used in patients on peritoneal dialysis. Serum fructosamine is a glycated protein that gives an estimation of glucose control over around 2 weeks, and measurement of this may be helpful in patients in whom HbA_{1c} is unreliable.

Table 1. Kidney Disease Improving Global Outcomes classification of chronic kidney disease using estimated glomerular filtration rate and albumin:creatinine ratio

Estimated glomerular filtration rate (ml/min/1.73m^2)	Albumin:creatinine ratio (mg/mmol)		
	0–3 (A1)	3–30 (A2)	>30 (A3)
>90 (G1)	G1A1	G1A2	G1A3
60–89 (G2)	G2A1	G2A2	G2A3
45–59 (G3a)	G3aA1	G3aA2	G3aA3
30–44 (G3b)	G3bA1	G3bA2	G3bA3
15–29 (G4)	G4A1	G4A2	G4A3
<15 (G5)	G5A1	G5A3	G5A3

G = glomerular filtration rate category (G1–G5), A = albumin:creatinine ratio category (A1–A3). From Levey et al (2011)

Challenges in management of hyperglycaemia in patients with chronic kidney disease

Chronic kidney disease is an insulin-resistant state, possibly because of the presence of uraemic toxins, excess parathyroid hormone or anaemia. Insulin sensitivity can be improved significantly by removal of uraemic toxins, administration of active vitamin D and correction of anaemia. A reduction in estimated glomerular filtration rate to below 20 ml/min/1.73m^2 may lead to a reduction in insulin clearance rate, leading to a significant risk of hypoglycaemia.

It is often noted that insulin requirements follow a biphasic course in progressive renal disease. In early renal impairment, insulin resistance predominates leading to increased insulin need. As renal impairment progresses, loss of clearance of insulin may lead to a falling insulin requirement, and a higher risk of hypoglycaemia requiring insulin dose reduction. Patients with chronic kidney disease stage 4 and below frequently suffer from anorexia, and hence the insulin dose requirement is further lessened.

Treatment options for patients with diabetes and renal impairment

Pharmacotherapy available to manage diabetes is significantly reduced in patients with chronic kidney disease because of a lack of data, risk of accumulation and concerns about hypoglycaemia.

Biguanides

Metformin is contraindicated in patients with an estimated glomerular filtration rate <30 ml/min/1.73m^2 because of the risk of accumulation. In patients with estimated glomerular filtration rate <45 ml/min/1.73m^2, metformin dose may have to be reduced (Chowdhury et al, 2015). In addition, patients should be counselled about avoiding metformin should they develop an intercurrent illness because of the risk of a sudden drop in renal function. Importantly, however, metformin should be restarted on recovery as its long-term cessation may lead to deterioration in glucose control and therefore more rapid decline in renal function. Metformin has not been trialled in the dialysis setting.

There is some concern about the possible link between metformin and lactic acidosis. While metformin overdose may be linked with lactic acidosis, a Cochrane review on the subject has suggested that there is no evidence from prospective or observational studies that metformin is associated with lactic

> “There is no hard evidence that tight glycaemic control reduces the rate of decline of renal function in patients with diabetes and renal impairment.”

KEY POINTS

- Diabetes is the leading cause of end-stage renal failure in many parts of the world.
- Chronic kidney disease in patients with diabetes is associated higher risk of cardiovascular and other complications.
- Glycaemic control is important, but glycaemic targets should be realistic and avoid hypoglycaemia, especially in patients with more severe chronic kidney disease.
- Interpretation of glycated haemoglobin (HbA_{1c}) in patients with chronic kidney disease may be difficult.
- Pharmacotherapy for hyperglycaemia is restricted in diabetic patients with chronic kidney disease.
- Diabetic patients with chronic kidney disease require multidisciplinary management with input from nephrologists and diabetes specialists.

acidosis, nor even associated with elevated lactate levels (Salpeter et al, 2010). A review of the General Practice Research Database showed a crude rate of lactic acidosis of 3.3 per 100 000 patient years in metformin users, compared to 4.8 per 100 000 patient years in sulfonylurea users (Bodmer et al, 2008).

Sulfonylureas and prandial glucose regulators

Sulfonylureas augment insulin secretion in a glucose-independent manner, so they can cause hypoglycaemia. Short-acting sulfonylureas, such as tolbutamide or gliclazide, may be used with caution in patients with chronic kidney disease, but reduction in dose may be required as renal function declines.

Meglitinides (nateglinide and repaglinide) are short-acting insulin secretagogues, and may cause less weight gain and hypoglycaemia than sulfonylureas. Repaglinide undergoes hepatic metabolism to inactive metabolites, and hence may be used in chronic kidney disease, with the attendant cautions required for using sulfonylureas.

Thiazolidinediones (glitazones)

Pioglitazone is a peroxisome proliferator-activated receptor-gamma (PPARγ) agonist that improves insulin sensitivity and beta cell function. It does not accumulate in patients with chronic kidney disease, so may be a potential therapeutic option, but this is limited by water retention and increased risk of heart failure. In addition, increased risk of post-menopausal fractures in women has been reported. Many patients with diabetes and chronic kidney disease may have cardiovascular disease, and hence use of pioglitazone requires caution.

Alpha-glucosidase inhibitors

Acarbose inhibits disaccharidases, hence reducing absorption of glucose from the gut. Drug levels and active metabolites are increased in chronic kidney disease, and acarbose is contraindicated in patients with estimated glomerular filtration rate <25ml/min/1.73m^2.

Dipeptidyl peptidase-4 inhibitors

Dipeptidyl peptidase-4 (DPP-4) inhibitors act by inhibiting the enzyme that breaks down glucagon-like peptide-1 (GLP-1), thereby increasing endogenous levels of GLP-1. GLP-1 stimulates insulin secretion and reduces appetite, and therefore is useful to aid weight loss. Most DPP-4 inhibitors are predominantly renally excreted, so require dose reduction in patients with chronic kidney disease. Linagliptin, however, is predominantly bile excreted, and can be used at unchanged doses in all stages of chronic kidney disease.

Glucagon-like peptide-1 analogues

GLP-1 analogues are useful in obese patients with diabetes, as they improve glucose control and reduce weight. They commonly cause nausea, bloating and other gastrointestinal disturbance, but liraglutide has a licence for use in patients with estimated glomerular filtration rates of 30 ml/min/1.73m^2 and above.

Sodium glucose transporter 2 inhibitors

This relatively new class of oral agent acts by blocking re-uptake of glucose in the proximal tubule, hence inducing glycosuria. A common side effect is polyuria, but also urinary tract infection and genital candidiasis are more common. The gliflozins are currently not licenced for commencement in patients with estimated glomerular filtration rate <45 ml/min/1.73m^2. In addition, concern over the possibility of inducing diabetic ketoacidosis in patients with type 2 diabetes has been reported (Taylor et al, 2015).

Insulin

Despite drawbacks of hypoglycaemia, weight gain and the need for self-monitoring of blood glucose, insulin remains an important therapy in patients with chronic kidney disease, because of the lack of other therapeutic options available. Insulin therapy may be given as a variety of regimens, but is most commonly commenced in type 2 diabetes as the addition of intermediate human insulin at night to other oral hypoglycaemic agents (Chowdhury et al, 2014). Insulin is titrated to fasting glucose levels, but if glycaemic control remains poor, or post-prandial hyperglycaemia is a problem, twice-daily fixed mixture insulin may be used, or the patient converted to a basal bolus regimen (rapid-acting insulin with meals, intermediate human insulin at night). Patients with chronic kidney disease who are using insulin therapy need careful education about self-monitoring, the risks of hypoglycaemia and the need for regular meals. Dose reduction is frequently required as renal function declines.

Screening and managing complications in diabetic patients with chronic kidney disease

Patients with diabetic nephropathy have much greater risk of developing other microvascular and macrovascular complications of diabetes, so they require regular monitoring and screening for complications such as retinopathy, foot disease and cardiovascular disease. Patients with estimated glomerular filtration rates under 40 ml/min/1.73m^2 may need to be seen in a combined multidisciplinary clinic involving diabetes and renal specialists (Tuttle et al, 2014). This may be usefully undertaken in a diabetic-renal clinic, with the aim of preventing or delaying the onset of end-stage renal failure.

Management of glucose in patients with end-stage renal disease

Renal replacement therapy can lead to significant difficulties in glycaemic management in diabetic patients with chronic kidney disease. In peritoneal dialysis, glucose is used as the main osmole, leading to significant periods of hyperglycaemia. A further difficulty is that changing peritoneal dialysis fluid prescriptions may lead to rapid changes in glucose levels day by day. Glycaemic variability is well recognized in such patients and can be challenging to manage.

> **Haemodialysis may affect insulin secretion, clearance and resistance as the result of periodic improvement in uraemia, acidosis and phosphate metabolism.**

Poor glycaemic control can lead to a vicious cycle of thirst and polydipsia, increasing fluid retention and the need for higher glucose concentration bags, leading to poorer glycaemic control. In the authors' experience, use of continuous blood glucose monitoring sensors may be helpful in managing such patients (Jin et al, 2015).

Haemodialysis, conversely, is often associated with rapid falls in blood glucose levels during a haemodialysis session. Haemodialysis may affect insulin secretion, clearance and resistance as the result of periodic improvement in uraemia, acidosis and phosphate metabolism. Furthermore, dialysis may affect the clearance of anti-hyperglycaemic therapy such as insulin or sulfonylureas. Therefore glucose control on dialysis days may be very different to that on non-dialysis days, leading to unpredictable glucose levels and glycaemic variability, which may require varying oral hypoglycaemic or insulin therapy according to day of dialysis (Abe and Kalantar-Zadeh, 2015).

Renal transplantation is the treatment of choice for patients with end-stage renal failure. Immunosuppression with steroids and other drugs such as tacrolimus can have potent adverse effects on glucose metabolism, and post-transplant diabetes (or new onset diabetes after transplantation) is a common phenomenon in such patients (Tufton et al, 2014). Patients with pre-existing diabetes frequently develop poorer glycaemic control during the early period after transplantation.

Conclusions

Diabetes in patients with chronic kidney disease is associated with poorer outcomes and high risk of death, morbidity and poorer quality of life. The aim of management should be to prevent or delay the onset of end-stage renal failure, and to screen for and manage other complications. Reduction of blood pressure and cardiovascular risk are the clinical priorities, but improvement in glycaemia remains important to try and reduce risk of progression, and prevent other complications. Glycaemic targets should be realistic, individualized, and take into account the high risk of hypoglycaemia, especially in more severe chronic kidney disease. Patients should be managed in a multidisciplinary manner with input from renal and diabetes specialists. **BJHM**

Conflict of interest: none.

TOP TIPS

- Be aware that the diabetic patient with albuminuria has a significantly increased risk of cardiovascular and microvascular complications, and that preventative therapy to reduce this risk is mandatory.
- Glucose control matters in people with diabetes and renal disease, but beware of very tight glucose control because of the adverse impact of hypoglycaemia on cardiovascular outcomes.
- Don't rely solely on monitoring of glucose control with glycated haemoglobin (HbA_{1c}) in people with renal impairment. The result may be difficult to interpret as a result of renal anaemia and other factors.
- Metformin should be continued until estimated glomerular filtration rate falls to 30 ml/min/1.73m^2 or below. The dose may need to be reduced if estimated glomerular filtration rate falls below 45 ml/min/1.73m^2.
- Patients on haemodialysis frequently become hypoglycaemic on dialysis days. Patients on peritoneal dialysis may have considerable glycaemic variability. Continuous glucose sensing may help improve glucose control and reduce hypoglycaemia.
- Patients with diabetes and significant renal impairment (chronic kidney disease stage 3b and below) need multidisciplinary management with diabetes and renal specialists.

Abe M, Kalantar-Zadeh K (2015) Haemodialysis-induced hypoglycaemia and glycaemic disarrays. *Nat Rev Nephrol* **11**: 302–13 (doi: 10.1038/nrneph.2015.38)

Action to Control Cardiovascular Risk in Diabetes Study Group (2008) Effects of Intensive Glucose Lowering in Type 2 Diabetes. *N Engl J Med* **358**: 2545–59 (doi: 10.1056/NEJMoa0802743)

Bodmer M, Meier C, Krahanbuhl S, Jick SS, Meier CR (2008) Metformin, sulphonylureas or other antidiabetic drugs and the risk of lactic acidosis or hypoglycaemia. *Diabetes Care* **31**: 2086–91 (doi: 10.2337/dc08-1171)

Chowdhury TA, Wright R, Charlton M (2014) Insulin for the uninitiated. *Clin Med* **14**: 623–9 (doi: 10.7861/clinmedicine.14-6-623)

Chowdhury TA, Wright R, Yaqoob MM (2015) Using metformin in the presence of renal disease. *BMJ* **350**: h1758 (doi: 10.1136/bmj.h1758)

DCCT/EDIC Research Group (2014) Effect of intensive diabetes treatment on albuminuria in type 1 diabetes: long-term follow-up of the Diabetes Control and Complications Trial and Epidemiology of Diabetes Interventions and Complications study. *Lancet Diabetes Endocrinol* **2**: 793–800 (doi: 10.1016/S2213-8587(14)70155-X)

Inzucchi S, Bergenstal RM, Buse JB et al (2012) Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach. Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* **35**: 1364–79 (doi: 10.2337/dc12-0413)

Jin YP, Su XF, Yin GP et al (2015) Blood glucose fluctuations in hemodialysis patients with end stage diabetic nephropathy. *J Diabetes Complications* **29**: 395–9 (doi: 10.1016/j.jdiacomp.2014.12.015)

Levey AS, de Jong PE, Coresh J et al (2011) Kidney Disease Improving Global Outcomes. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. *Kidney Int* **80**: 17–28 (doi: 10.1038/ki.2010.483)

National Institute for Health and Clinical Excellence (2015) Type 2 diabetes: the management of Type 2 diabetes. NICE Guidelines CG87. www.nice.org.uk/guidance/cg87/chapter/1-recommendations#kidney-damage (accessed 23 June 2015)

Parving HH, Rossing P (2015) Diabetic nephropathy in 2014: improved cardiorenal prognosis in diabetic nephropathy. *Nat Rev Nephrol* **11**: 68–70 (doi: 10.1038/nrneph.2014.238)

Reidy K, Kang HM, Hostetter T, Susztak K (2014) Molecular mechanisms of diabetic kidney disease. *J Clin Invest* **124**: 2333–40 (doi: 10.1172/JCI72271)

Renal Association (2014) UK Renal Registry Seventeenth Annual Report 2014. www.renalreg.org/reports/2014-seventeenth-annual-report/ (accessed 23 June 2015)

Salpeter SR, Greyber E, Pasternak GA, Salpeter EE (2010) Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes. *Cochrane Database Syst Rev* **4**: CD002967 (doi: 10.1002/14651858.CD002967.pub4)

Taylor SI, Blau JE, Rother KI (2015) Perspective: SGLT2 inhibitors may predispose to ketoacidosis. *J Clin Endocrinol Metab* **18**: jc20151884 (doi: 10.1210/jc.2015-1884)

Tufton N, Ahmad S, Rolfe C, Rajkariar R, Byrne C, Chowdhury TA (2014) New-onset diabetes after renal transplantation. *Diabet Med* **31**: 1284–92 (doi: 10.1111/dme.12534)

Tuttle KR, Bakris GL, Bilous RW et al (2014) Diabetic kidney disease: a report from an ADA Consensus Conference. *Am J Kidney Dis* **64**: 510–33 (doi: 10.1053/j.ajkd.2014.08.001)

UKPDS Study Group (1998) Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS33). *Lancet* **352**: 837–53

Yamout H, Lazich I, Bakris GL (2014) Blood pressure, hypertension, RAAS blockade, and drug therapy in diabetic kidney disease. *Adv Chronic Kidney Dis* **21**: 281–6 (doi: 10.1053/j.ackd.2014.03.005)