

# Diabetes mellitus in dialysis and renal transplantation

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*Ther Adv Endocrinol Metab*

2021, Vol. 12: 1–16

DOI: 10.1177/  
20420188211048663

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**Abstract:** Diabetes mellitus is the commonest cause of end-stage kidney failure worldwide and is a proven and significant risk factor for the development of cardiovascular disease. Renal impairment has a significant impact on the physiology of glucose homeostasis as it reduces tissue sensitivity to insulin and reduces insulin clearance. Renal replacement therapy itself affects glucose control: peritoneal dialysis may induce hyperglycaemia due to glucose-rich dialysate and haemodialysis often causes hypoglycaemia due to the relatively low concentration of glucose in the dialysate. Autonomic neuropathy which is common in chronic kidney disease (CKD) and diabetes increases the risk for asymptomatic hypoglycaemia. Pharmacological options for improving glycaemic control are limited due to alterations to drug metabolism. Impaired glucose tolerance and diabetes are also common in the post-kidney-transplant setting and increase the risk of graft failure and mortality. This review seeks to summarise the literature and tackle the intricacies of glycaemic management in patients with CKD who are either on maintenance haemodialysis or have received a kidney transplant. It outlines changes to glycaemic targets, monitoring of glycaemic control, the use of oral hypoglycaemic agents, the management of severe hyperglycaemia in dialysis and kidney transplantation patients.

**Keywords:** diabetes mellitus, dialysis, kidney transplantation, management

Received: 14 May 2021; revised manuscript accepted: 29 August 2021.

## Introduction

Diabetes mellitus (DM) and end-stage kidney failure (ESKF) are both common conditions that impact significantly on duration and quality of life. DM is the most common cause of chronic kidney disease (CKD) world-wide.<sup>1</sup> DM and CKD are both independent risk factors for the development of cardiovascular disease;<sup>2,3</sup> therefore, glycaemic control in ESKF is of significant prognostic importance.

Management of DM in patients on dialysis is complicated by multiple factors. Alterations to carbohydrate and insulin metabolism as well as the pharmacokinetics of hypoglycaemic agents result in significant glycaemic variability. Monitoring of glycaemic control can be challenging and serum glucose levels are impacted by ESKF treatment, for example, the high glucose load in peritoneal dialysis fluid and fixed glucose concentration in haemodialysis fluid (dialysate).

In addition, treatment of diabetic emergencies such as severe hyperglycaemia and diabetic ketoacidosis (DKA) is more complex in the oliguric or anuric patient.

The purpose of this review article is to aid the clinician managing patients with diabetes who are dialysis-dependent and post kidney transplantation. It will summarise the changes to physiology, monitoring of glycaemic control, the goals of therapy, pharmacological interventions for diabetes and management of diabetic emergencies in patients with ESKF.

## Glucose homeostasis in CKD

The kidneys play an important role in glucose homeostasis.

In the healthy kidney, insulin is freely filtered at the glomerulus to enter Bowman's capsule.

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Additional insulin then enters the nephron *via* simple diffusion from peritubular vessels. Insulin within the proximal convoluted tubule is transported *via* carrier-mediated endocytosis into the peri-luminal cells where it is packaged into lysosomes and metabolised into amino acids.<sup>4</sup> Assuming a normal glomerular filtration rate (GFR) of 120 ml/min, insulin is renally cleared at a rate of 200 ml/min. In CKD, a reduction in the rate of insulin clearance is only observed once there has been a significant reduction in the GFR.<sup>5</sup> This is because diffusion of insulin from peritubular vessels compensates for the reduction in glomerular filtration. Once the GFR has fallen to around 15–20 ml/min, insulin degradation declines rapidly, creating a significant risk of hypoglycaemia.<sup>6</sup>

CKD gives rise to a state of insulin resistance. This is thought to be predominantly due to the effects of uraemia.<sup>5,7</sup> Unlike the slowing down of insulin degradation, which occurs late in CKD, insulin resistance is observed even in patients with only mild-to-moderate renal impairment.<sup>8</sup> Increased insulin resistance seems to predominantly affect the insulin-mediated effects on glycogen synthesis. The role of insulin in increasing cellular uptake of potassium and promoting proteolysis remains unchanged.<sup>9,10</sup> The use of insulin infusions is therefore an effective intervention for promoting intra-cellular shifting of potassium in the emergency management of hyperkalaemia in the ESKF patient. Renal replacement therapy has been shown to improve tissue sensitivity to insulin.<sup>11</sup> This supports the hypothesis that insulin resistance in ESKF is caused by uraemia. Calcitriol deficiency in ESKF has also been shown to play a role in causing insulin resistance. Several small trials have demonstrated that intravenous calcitriol improves glucose tolerance in haemodialysis patients, independent of plasma calcium and parathyroid hormone level.<sup>12–14</sup> It is unknown whether this effect is mediated by calcitriol itself or reversal of hyperparathyroidism.

In order to compensate for reduced tissue sensitivity to insulin, the pancreatic beta cells would need to increase insulin secretion. In many patients with CKD, insulin secretion does not increase, resulting in worse glucose tolerance. Suppression of insulin release is thought to occur due to multiple factors, including acidosis.<sup>7</sup> Secondary hyperparathyroidism is also thought to play a role<sup>15</sup> – this may be due to increased

intracellular calcium, which reduces intracellular adenosine triphosphate (ATP) and activity of sodium-potassium-ATPase.<sup>16</sup> Studies in animals suggest that these changes to physiology can be prevented by prior parathyroidectomy or by using a calcium-channel blocker.<sup>17</sup>

In summary, CKD affects glucose homeostasis in different ways as renal function declines. Insulin resistance is a feature of progressive CKD, meaning a greater amount of insulin is required to promote glycogenesis and reduce serum glucose levels. Once the GFR falls to around 20 ml/min, the rate at which insulin is degraded and cleared begins to decrease. Clinically, this translates into a biphasic pattern of insulin requirement. Initially patients require more insulin due to increased resistance to insulin. This is followed by reduced insulin requirements as insulin clearance decreases. Careful monitoring of glycaemic control is of utmost importance due to changes in glucose-handling with disease progression.

Patients with CKD and diabetes are prone to gastroparesis, which can delay the surge in glucose seen after meals, as well as delay absorption of antidiabetic medication. This complicates the timing of administration of insulin and oral agents.<sup>18</sup> Patients with significant glycaemic variability may benefit from gastric-emptying studies.

### Effects of dialysis on glycaemic control

Maintenance haemodialysis complicates glycaemic control as it leads to large glycaemic variability on dialysis days.

Haemodialysis affects glucose homeostasis in multiple ways. First, it clears glucoregulatory hormones such as insulin and glucagon.<sup>19</sup> Second, it affects insulin secretion and resistance due to periodic resolution of uraemia, hyperphosphataemia and acidosis. The glucose concentration in the dialysate solution also influences glucose control. Low concentrations of glucose in dialysate will cause glucose to diffuse from plasma to dialysate across a concentration gradient. This may result in hypoglycaemia. In a large prospective study, 10.5% of 19,849 patients starting haemodialysis had a severe hypoglycaemic episode in their first year.<sup>20</sup> Doses of antidiabetic medication, especially insulin, are often reduced for patients on dialysis days in order to prevent hypoglycaemia. Frequent or persistent hypoglycaemia

is often a result of inadequate dialysis and calorie intake. It may also suggest an occult infection or malignancy. Symptomatic hypoglycaemia during dialysis may affect compliance with therapy.

Unlike the dialysate in haemodialysis, peritoneal dialysate has higher glucose concentrations than blood. To facilitate ultrafiltration, peritoneal dialysate is purposefully rendered hyperosmolar in order to promote shifting of water *via* osmosis from plasma to peritoneal fluid. Glucose is often used as the osmolar agent. Consequently, glucose can be absorbed from the dialysate into the circulation, causing a rise in glucose levels during peritoneal dialysis. This contributes to chronic glycaemia and in patients who are high transporters, it can cause severe hyperglycaemia. In these patients, rapid glucose absorption also lowers the osmotic gradient between dialysate and blood, resulting in inadequate dialysis. Patients receiving peritoneal dialysis with uncontrolled hyperglycaemia should undergo peritoneal equilibration testing.

### Monitoring glycaemic control in ESKF

Measurement of glycated haemoglobin (HbA1c) level is the standard method for assessing long-term glycaemic control. It measures average glucose levels over approximately 3 months. Clinicians must remain aware of factors that render HbA1c less reliable in patients on haemodialysis. It is important to note that CKD patients were excluded from the Diabetes Control and Complications Trial, which demonstrated the relationship between HbA1c and average glucose level. Inaccuracies of HbA1c measurement occur due to laboratory and patient factors.

Elevated concentrations of urea in ESKF impair the accuracy of laboratory tests for measurement of HbA1c such as agar gel electrophoresis. Reliable techniques for HbA1c measurement in ESKF include Boronate-agarose affinity chromatography<sup>21</sup> and the thiobarbituric acid method.<sup>22</sup>

Patient factors that impair the accuracy of HbA1c are related to the lifespan of haemoglobin. It is useful to understand that the longer an erythrocyte lives, the more it will become glycated, irrespective of the actual average glucose level during this time. Factors which lead to underestimation of HbA1c are reduced erythrocyte lifespan due to uraemia;<sup>23</sup> blood transfusions;<sup>24</sup> and the use of

erythropoietin<sup>25</sup> which increases the proportion of young erythrocytes. In contrast, factors which lead to overestimation of HbA1c are uraemia, which increases the rate of non-enzymatic haemoglobin glycosylation;<sup>26</sup> increased urea nitrogen levels, which increase the level of carbamylated haemoglobin – many HbA1c assays do not differentiate between carbamylated and glycated haemoglobin;<sup>27</sup> iron-deficiency;<sup>28</sup> and metabolic acidosis.<sup>29</sup>

Despite the limitations, in patients with good-to-moderate glycaemic control (HbA1c 42–53 mmol/mol), HbA1c seems to estimate glycaemic control similarly to those without CKD.<sup>30</sup>

Glycated albumin has been proposed as a method of monitoring glycaemic control in diabetic patients with CKD. It reflects glycaemia over a shorter duration than HbA1c of approximately 2–4 weeks. It is associated with all-cause and cardiovascular mortality in patients on maintenance haemodialysis;<sup>31,32</sup> however, it is limited by hypoalbuminaemia which is common in patients with CKD.<sup>33</sup> There is limited data to support the use of glycated albumin in CKD. Larger studies evaluating its use in this population need to be performed before its use can be recommended.

Continuous glucose monitoring (CGM) with a monitor or intermittent self-monitoring of glucose provides useful information of glycaemia not affected by CKD or haemodialysis. In patients in whom HbA1c is unreliable, such as those on dialysis, CGM measurements can be used to calculate an average blood glucose that can then be expressed in the units of HbA1c (%). This is known as the Glucose Management Indicator (GMI). Clinicians can work with patients to create glucose targets using GMI.<sup>34,35</sup> CGM may be used long term in patients receiving insulin as it not only provides information on glycaemic variability, it also alerts to hypoglycaemia. In patients who do not take insulin, intermittent capillary glucose monitoring may be used for a short time period to get insight into average blood glucose and whether this is accurately reflected by HbA1c in the individual patient. The Joint British Diabetes Society supports the use of CGM but recommends that the device be calibrated on a non-dialysis day to minimise calibration issues caused by rapid changes in blood glucose due to the dialysis process.<sup>36</sup>

### Goals of therapy in ESKF with DM

The target HbA1c associated with greatest survival in haemodialysis patients is unknown. Despite the aforementioned factors that impact its reliability, a higher HbA1c is associated with a greater risk of mortality in haemodialysis patients. A meta-analysis of 10 observational studies (83,364 patients) showed that, compared with an HbA1c level of 48–57 mmol/mol, HbA1c over 69 mmol/mol is associated with higher mortality.<sup>37</sup>

The CKD subgroup study of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial demonstrated that patients with CKD who received intensive glycaemic management were at greater risk for both cardiovascular and all-cause-mortality compared with patient with normal renal function. This is thought to occur due to greater incidence of severe hypoglycaemia, which is associated with mortality.<sup>38</sup>

A prospective cohort study of 9201 haemodialysis patients with either type 1 or type 2 diabetes showed the lowest risk of mortality with a target HbA1c of 53–65 mmol/mol. Mortality increased as HbA1c moved either higher or lower than this range.<sup>39</sup>

Target HbA1c in patients with diabetes on haemodialysis should be individualised based on the presence of comorbid conditions and the risk of hypoglycaemia. The Joint British Diabetes Societies for Inpatient Care advise a target HbA1c of 56–68 mmol/mol if the patient is on hypoglycaemia-inducing treatment.<sup>36</sup> This is higher than the target in non-CKD diabetic patients of 53 mmol/mol.

### Severe hyperglycaemia in ESKF

Severe hyperglycaemia is a serious complication in diabetic patients. As patients with ESKF are either oliguric or anuric, the severe dehydration and hypernatraemia seen in the hyperosmolar hyperglycaemic state (HHS) due to diuresis does not occur. Therefore, ESKF patients with severe hyperglycaemia tend to be asymptomatic.<sup>40</sup> A major concern in these patients is that, due to extracellular hypertonicity, potassium and fluid may shift extracellularly to cause hyperkalaemia and acute intravascular volume expansion.<sup>41</sup>

Due to oliguria or anuria, ESKF patients with DKA tend to be protected from the severe dehydration seen with DKA in preserved renal function.

Rather than a focus on fluid resuscitation, management consists of intravenous insulin infusion with close monitoring of serum glucose and potassium. Due to severe hyperglycaemia, patients are presumed to be hyperkalaemic and should not receive intravenous potassium-containing fluids.

### Summary of DM in ESKF

The physiological changes that influence glycaemic control in ESKF are reduced insulin sensitivity and inadequate insulin secretion. These are offset by reduced renal clearance of insulin. Haemodialysis increases sensitivity to insulin and also reduces glucose levels *via* a concentration gradient. This makes patients on insulin who receive haemodialysis particularly susceptible to hypoglycaemia.

Monitoring of long-term glycaemia in ESKF with HbA1c is less reliable than in the general population due to factors which influence the erythrocyte lifespan. Though other methods, such as glycated albumin, exist for monitoring glycaemic control, HbA1c is still the preferred method. Direct glucose measurements are most useful as they also provide information on glycaemic variability and alert patients to hypoglycaemia. The GMI translates the average capillary blood glucose measurement to the units of HbA1c. A target HbA1c of 56–68 mmol/mol is recommended in most patients, though the cardiovascular benefits of achieving this target need to be weighed against the risk of hypoglycaemia on an individual basis.

### Post-transplantation diabetes mellitus

Post-transplantation diabetes mellitus (PTDM) describes the presence of DM post kidney transplantation, irrespective of the onset of DM.<sup>42</sup> This therefore includes patients that may have had undiagnosed DM prior to kidney transplantation. It differs from the older term new-onset diabetes mellitus after transplant (NODAT), which excludes patients who may have had DM prior to transplantation.<sup>43</sup> PTDM excludes patients who develop transient hyperglycaemia after transplantation due to postsurgical stress or high-dose glucocorticoids. Our understanding of the epidemiology of PTDM has been complicated by lack of clear diagnostic criteria. Using current criteria, it is estimated that up to one-third of non-diabetic kidney transplant recipients

develop impaired glucose tolerance or PTDM at 6 months.<sup>44–47</sup> There were no clear criteria for the diagnosis of PTDM until the first PTDM consensus guideline in 2003.<sup>43</sup> Multiple studies have shown that PTDM is associated with increased cardiovascular mortality post-transplantation.<sup>48–52</sup> PTDM also significantly reduces allograft survival, though this is thought to be primarily due to mortality.<sup>50,51</sup> An understanding of PTDM and its management is essential.

#### *Risk factors of PTDM*

Multiple risk factors for the development of PTDM have been identified. These can be categorised into either modifiable or non-modifiable.

Pre-operative impaired glucose tolerance has been shown to increase the risk of developing PTDM. In a study of 120 transplant recipients, impaired glucose tolerance, diagnosed by Oral Glucose Tolerance Test (OGTT), pre-transplantation was associated with a relative risk of 2.4 [95% confidence interval (CI) 1.1–5.3] for development of NODAT.<sup>53</sup> Hyperglycaemia in the peri-operative period also increases the risk for PTDM. In a retrospective study of 377 non-diabetic kidney transplant recipients, 30% of the 327 patients requiring insulin therapy during their admission developed NODAT. Only 4% of patients without inpatient hyperglycaemia developed NODAT. In adjusted analyses, requirement of insulin during admission for a kidney transplant conferred a relative risk of 4.01 (95% CI 1.49–10.7,  $p < 0.05$ ) for the development of NODAT.<sup>54</sup> Tight glycaemic control in the post-operative period may reduce the risk of developing PTDM. A study of 50 renal transplant recipients assigned to either standard treatment [short-acting insulin or an oral hypoglycaemic agent (OHA) for evening blood glucose of 10–14 mmol/L] or isophane insulin for blood glucose over 7.8 mmol/L demonstrated a 73% risk reduction for PTDM at 1 year with early isophane insulin. This is thought to occur due to insulin-mediated beta-cell protection.<sup>55</sup>

Obesity is an independent risk factor for the development of PTDM. In a retrospective cohort study of 15,309 transplant recipients, 14.1% of the 3533 patients with a body mass index (BMI) greater than 30 developed NODAT, compared with 7.8% of 6498 patients with a BMI under 25. In this study, a BMI greater than 30 compared

with a BMI under 25 conferred a relative risk of 1.85 (95% CI 1.63–2.08) for development of PTDM.<sup>56</sup>

Immunosuppressant medication post-transplantation is associated with the development of PTDM. Glucocorticoids have a dose-dependent association with PTDM. A prospective cohort study of 173 consecutive kidney transplant recipients showed that every 0.1 mg/kg per day higher dose of prednisolone increased the risk of developing PTDM at 10 weeks post-transplant by 5%.<sup>57</sup> Tacrolimus, cyclosporine and sirolimus have also been shown to increase the risk of PTDM.<sup>58–61</sup> A tacrolimus level greater than 15 ng/ml significantly increases the risk of PTDM.<sup>58</sup> Mycophenolate mofetil (MMF) reduce the risk of PTDM. A retrospective study showed a relative risk for development of PTDM of 0.84 (95% CI 0.72–0.97) with azathioprine and 0.78 (95% CI 0.69–0.88) with MMF.<sup>62</sup> This risk reduction may be due to lower steroid use and avoidance of tacrolimus.

Hepatitis C virus (HCV) infection increases the risk for PTDM. In a meta-analysis including 2502 renal transplant recipients, HCV seropositivity was associated with an odds ratio of 3.97 (95% CI 1.83–8.61) of developing PTDM.<sup>63</sup> The mechanism *via* which HCV increases propensity towards insulin resistance is not fully explained however is likely due to hepatocyte destruction, which reduces availability of hepatically produced insulin-receptor substrates and hepatic glycogen production.<sup>63</sup> HCV therapy prior to transplantation may prevent PTDM.<sup>64</sup>

Non-modifiable risk factors for PTDM include age, Hispanic, south-Asian or black ethnicity, male and deceased donor grafts, family history of type 2 DM and increased human leukocyte antigen mismatching.<sup>56,57,62,65,66</sup> An analysis of 15,309 patients demonstrated a 29% increase in relative risk for PTDM for every 10-year age increment.<sup>56</sup>

#### *Pathogenesis of PTDM*

PTDM is thought to arise due to an interplay of reduced insulin secretion and increased insulin resistance. The relative impact of these is likely to be heterogenous across patients and affected by time-from-transplant. Reduced insulin secretion is generally considered to play a more fundamental role in the pathogenesis of PTDM. A retrospective

cohort study of 1064 stable renal transplant recipients found insulin secretion decreased and insulin sensitivity increased in transplant recipients compared with over 1000 non-transplant controls.<sup>67</sup> A 6-year prospective study of 63 renal transplant recipients found decreased insulin secretion to be the major mechanism by which PTDM occurs.<sup>68</sup>

The role of immunosuppressive agents in PTDM has been discussed in the previous section. A prospective longitudinal study of 18 renal transplant recipients receiving tacrolimus demonstrated a reduction in insulin secretion without a change in insulin resistance. A reduction in the trough tacrolimus level from 9.5 ng/ml to 6.4 ng/ml increased beta-cell secretion. This supports the notion that the effect of tacrolimus on glucose homeostasis is dose-dependent.<sup>69</sup>

#### *Screening and diagnosis of PTDM*

The 2014 international consensus meeting on post-transplantation DM defines criteria for the diagnosis of PTDM.<sup>42</sup> Hyperglycaemia is very common in the early post-transplant period.<sup>70</sup> Although this may increase the risk of developing PTDM, many cases are transient. It is therefore only possible to formally diagnose PTDM 6-weeks post-transplantation.<sup>42</sup> The Association of British Clinical Diabetologist and Renal Association (ABCD-RA) guidelines on the detection and management of PTDM advise screening for PTDM with afternoon capillary blood glucose in the early post-operative period. Patients with afternoon hyperglycaemia should undergo OGTT when clinically stable.<sup>71</sup> The reason for afternoon testing is that hyperglycaemic peaks tend to occur in the afternoon.<sup>72</sup>

The diagnostic criteria for PTDM have been adopted from the American Diabetes Association guidelines for diagnosing DM in the general population.<sup>73</sup> The gold-standard test for diagnosing PTDM is the OGTT. In addition to diagnosing PTDM, it is able to identify patients with impaired glucose tolerance (IGT). IGT is a pre-diabetes condition that is an independent predictor of mortality in transplant recipients.<sup>74</sup> The diagnosis of IGT is made by a plasma glucose of 7.8–11.0 mmol/L 2 hours after oral glucose intake.<sup>73</sup>

In 2009, the World Health Organization and American Diabetes Association adopted HbA1c as a diagnostic marker for DM.<sup>75</sup> HbA1c is a

marker of glucose levels over a prolonged period. Unlike the OGTT, it involves a single, untimed blood test and does not require patients to be fasted. Due to factors previously outlined in this review, HbA1c can be unreliable in CKD. Factors such as anaemia, estimated to be present in 52% of patients with CKD stage 4 and diabetes,<sup>76</sup> impact the reliability of HbA1c in CKD and may persist into the post-transplant period. Despite this, HbA1c measurement 90 days after transplantation has been shown to be predictive of PTDM at 1 and 3 years post-transplant.<sup>77</sup> Although specific in this setting, a meta-analysis of 2057 kidney recipients demonstrated poor sensitivity of HbA1c for diagnosing PTDM.<sup>78</sup> If performed at 1-year post-transplant, a combination of fasting plasma glucose and HbA1c is as effective as OGTT at diagnosing PTDM.<sup>79</sup>

#### *Glycaemic targets in PTDM*

As there is no high-level evidence to support the use of stringent glycaemic targets in patients post-transplantation, the ABCD-RA advises the same targets as for type 2 diabetes<sup>71</sup> (Table 1). The National Institute for Health and Care Excellence (NICE) suggests individualising the glycaemic target to the patient. It advises a more relaxed target in patients who are unlikely to achieve long-term risk reduction, are at risk of polypharmacy or in whom intensive management is not appropriate.<sup>80</sup>

#### *Altering immunosuppression in PTDM*

There is significant debate regarding the alteration of immunosuppression to prevent PTDM. The risk of PTDM needs to be balanced against the risk of graft rejection. The 2003 International Expert Panel International Consensus Guidelines,<sup>43</sup> KDIGO<sup>81</sup> and the Renal Association<sup>82</sup> have previously supported the modification of immunosuppression to prevent PTDM. Subsequent guidelines have stated that the choice of immunosuppressant agents should be primarily to prevent rejection, rather than PTDM.<sup>83</sup>

There is conflicting evidence regarding the benefit of corticosteroid sparing for prevention of PTDM. A 2017 Cochrane review of 7800 patients demonstrated an increased risk of acute withdrawal with steroid-sparing, with no benefit with regard to PTDM prevention.<sup>84</sup> Multiple other large studies show that steroid-avoidance can be

**Table 1.** Glycaemic targets in patients with diabetes and diabetic-nephropathy CKD.

	Glycaemic target (mmol/mol)	Note
Type 1 diabetes	48–58	Younger patients within 10 years duration of diabetes and variable microalbuminuria – CKD stage 2
	58–62	The majority of patients with proteinuria and/or CKD stages 3–4
	56–68	Patients with CKD stage 5 – dialysis
Type 2 diabetes	48–58	Majority of patients aged <40, or have CKD stages 1–2 (no basis to aim for 52 mmol/mol unless the patient is aged <40 and has CKD stages 1–2)
	52–58	For those with CKD stages 3–4 this target may be appropriate with a GLP-1 analogue or SGLT-2 inhibitor based treatment regimen without insulin
	58–68	For those with CKD stages 3–4 – proteinuria who are on an insulin-based regimen, and those with CKD stage 5 who are on dialysis

ABCD-RA, Association of British Clinical Diabetologist and Renal Association; CKD, chronic kidney disease; GLP-1, glucagon-like peptide-1; SGLT-2, sodium-glucose cotransporter-2.  
ABCD-RA recommends using these targets in patients post renal transplant.<sup>71</sup>

used to prevent PTDM.<sup>85–88</sup> A randomised trial supports the use of split-dosing of corticosteroids to reduce glycaemic variability and hyperglycaemia after renal transplantation.<sup>89</sup> A retrospective study of 298 renal transplant recipients has demonstrated that early withdrawal of steroids in low risk patients who have received basiliximab induction and are taking tacrolimus and MMF is effective is safe and effective at limiting graft rejection.<sup>90</sup> The effects of individual immunosuppressant agents on glycaemia is outline in Figure 1, which is a visual adaptation of the information from the ABCD-RA Guidelines on the Detection and Management of Diabetes Post Solid Organ Transplantation.<sup>71</sup>

### Oral hypoglycaemic agents in dialysis and kidney transplant patients

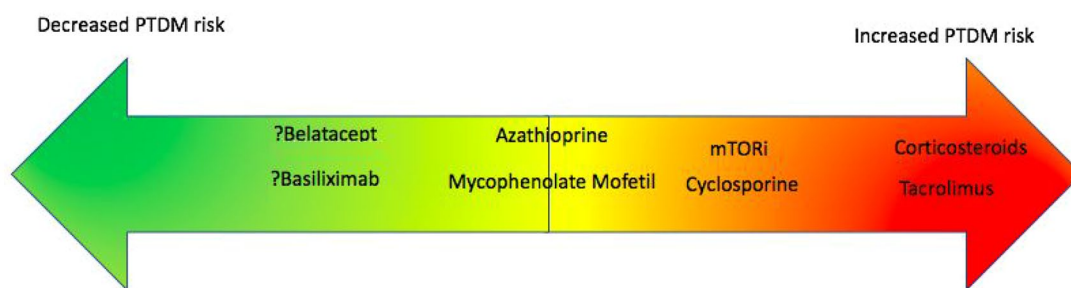
While insulin is the only therapy available for type 1 DM, there are multiple OHAs that may be used in type 2 DM. Unfortunately, some of these agents are unsuitable in patients on maintenance haemodialysis. It is important to have an understanding of the metabolism of OHAs and how this is affected by dialysis. Furthermore, there is

the potential for interactions between immunosuppressants and OHAs in patients post-transplant. The OHA classes and their utility in ESKF or post-transplantation will be discussed below. The OHAs and their use in haemodialysis and for PTDM are summarised in Table 2.

#### Sulfonylureas

Sulfonylureas stimulate pancreatic secretion of endogenous insulin by binding ATP-sensitive potassium channels on beta cells. They also increase sensitivity to insulin in fat and muscle cells. Circulating sulfonylureas are strongly bound to proteins such as albumin therefore are not readily cleared by haemodialysis.<sup>91</sup> Thus, sulfonylureas may accumulate in patients on haemodialysis and cause hypoglycaemia. Sulfonylureas should be avoided in patients on haemodialysis.

Sulfonylureas may be used in the post-transplant period; however, due to the risk of hypoglycaemia with reducing doses of immunosuppression, patients taking sulfonylureas must carefully monitor their blood glucose levels.<sup>75</sup>



**Figure 1.** Effects of immunosuppressive agents on PTDM risk, visual adaptation of 2021 ABCD-RA guidelines on the detection and management of diabetes post solid organ transplantation.<sup>71</sup>

**Table 2.** Oral hypoglycaemic agents and their use in HD or for PTDM.

Oral hypoglycaemic agent	Mechanism of action	Use in HD	Use in PD	Use post-transplant
Sulfonylureas	Stimulate endogenous insulin secretion. Increase sensitivity to insulin in fat and muscle cells	Avoid	May be used however requires close glycaemic monitoring	May be used but requires regular monitoring of blood glucose due to risk of hypoglycaemia
Meglitinides	Promote secretion of endogenous insulin	Avoid	May be used however requires close glycaemic monitoring	May be used but evidence is limited
Metformin	Decreases hepatic gluconeogenesis and increases peripheral insulin-mediated glucose utilisation.	Avoid	Avoid	May be used with eGFR > 30 ml/min. Beware of risk of lactic acidosis in AKI.
DPP-4 inhibitors	Reduce deactivation of incretins	Can be used. Dose adjustment may be required.	Can be used. Dose adjustment may be required.	May be used
GLP-1 analogues	Mimic the incretin GLP-1 to stimulate glucose-dependent insulin secretion	Avoid	Avoid	May be used
Pioglitazone	Increase tissue sensitivity to insulin	Unlikely to be dialysed. Requires careful monitoring.	Unlikely to be dialysed. Requires careful monitoring.	May be used
SGLT-2 inhibitors	Increase glycosuria	Avoid	Avoid	May be used. Beware increased risk of urinary tract infection.

AKI, acute kidney injury; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; HD, haemodialysis; PD, peritoneal dialysis; PTDM, post-transplantation diabetes mellitus; SGLT-2, sodium-glucose cotransporter-2.

### Meglitinides

Meglitinides act similarly to sulfonylureas in that they also promote secretion of endogenous insulin. Repaglinide and nateglinide are both metabolised by the liver. Repaglinide is then eliminated faecally (10% excreted renally) whereas nateglinide is

eliminated in the urine. Due to accumulation of metabolites, nateglinide may cause prolonged hypoglycaemia.<sup>92-94</sup> Meglitinides are also highly protein-bound therefore unlikely to be cleared *via* haemodialysis. There is limited evidence for their use in the haemodialysis population.



Repaglinide has been shown to be effective for PTDM. A small observational study of 23 patients showed a mean HbA1c reduction from 7.6% to 5.8% in 14 patients. The remaining patients required insulin.<sup>95</sup>

### *Biguanides*

Metformin is a very commonly used OHA in the non-CKD diabetic population. It is excreted in the urine and accumulation can cause lactic acidosis.<sup>96</sup> It should therefore be avoided in patients with ESKF.<sup>94</sup>

Metformin should be used as first-line therapy in transplant recipients with an estimated glomerular filtration rate (eGFR) >30 ml/min and BMI >25 kg/m<sup>2</sup>. A retrospective analysis of 14,144 renal transplant recipients with pre-transplant diabetes demonstrated significantly reduced malignancy- and infection-related mortality in patients taking metformin.<sup>97</sup> A further observational study of 46,914 recipients demonstrated improved better graft survival and reduced mortality in patients taking metformin.<sup>98</sup> Due to the risk of lactic acidosis in acute kidney injury, metformin must be temporarily suspended in post-transplant patients who become unwell.

### *DPP-4 inhibitors*

DPP-4 inhibitors act by reducing the deactivation of incretins, which promote insulin secretion in response to an oral glucose load. They cause a glucose-dependent increase in insulin. They do not cause hypoglycaemia and are recommended for use in haemodialysis, though dose-adjustments are required for sitagliptin, vildagliptin and alogliptin.<sup>36</sup> Linagliptin is mostly excreted faecally and only minimally in the urine.<sup>99,100</sup> It is not cleared by haemodialysis; therefore, no adjustment is needed for patients on haemodialysis.<sup>101</sup>

A 2019 meta-analysis of five studies investing gliptin use in patients with PTDM after renal transplant suggested that they are safe and effective at reducing HbA1c without affecting eGFR or tacrolimus level.<sup>102</sup>

### *GLP-1 analogues*

GLP-1 analogues mimic the incretin GLP-1 to stimulate glucose-dependent insulin secretion.

They also delay gastric emptying, suppress appetite and suppress glucagon levels.<sup>103</sup>

There is limited data available on GLP-1 analogues in ESKF and haemodialysis; therefore, their use is not recommended in this setting.<sup>104</sup>

Although there is limited data available for the use of GLP-1 analogues post-transplant, there is some evidence from small case series to suggest that they may be effective at reducing glucose levels and weight, without affecting tacrolimus levels.<sup>105,106</sup> A Norwegian study of 12 renal transplant recipients with PTDM demonstrated that infusion of GLP-1 analogue reduces the glucose-induced glucagon suppression seen in PTDM.<sup>107</sup> In addition, in a retrospective analysis of 63 patients with PTDM after solid organ transplantation, dulaglutide was effective at inducing weight loss, reducing BMI and insulin requirement.<sup>108</sup>

### *Thiazolidinediones (TZDs)*

TZDs act by binding and activating peroxisome proliferator-activated receptor (PPAR) gamma. This increases glucose utilisation by adipose and muscle in response to insulin and also suppresses hepatic gluconeogenesis.<sup>109</sup> TZDs have been associated with oedema formation and heart failure.<sup>110</sup> This is of particular importance in patients with ESKF who are already at high risk of heart failure and fluid overload. There is conflicting evidence regarding the survival benefit of TZDs in haemodialysis. Rosiglitazone has been shown to increase all-cause and cardiovascular mortality in patients on haemodialysis.<sup>111</sup> Due to its adverse cardiovascular safety profile, rosiglitazone was withdrawn from the market in the United Kingdom in 2010. A larger study showed that in haemodialysis patients not taking insulin, survival improves with the addition of a TZD.<sup>112</sup>

Pioglitazone is the only remaining TZD available for use in the United Kingdom. It is almost entirely metabolised by the liver; therefore, it does not require dose adjusting in renal impairment.<sup>94</sup> Its use is not licenced for patients on dialysis.

A randomised controlled trial of 83 non-diabetic renal allograft recipients demonstrated that the addition of pioglitazone reduces the progression of carotid intima-media thickness and improves insulin resistance.<sup>113</sup>

### Alpha-glucosidase inhibitors

Alpha-glucosidase inhibitors such as acarbose reduce post-prandial glucose peaks by reducing gastrointestinal absorption of glucose. Their use in severe renal impairment has not been examined; therefore, they are not recommended for use in patients with advanced CKD.<sup>94</sup>

### SGLT2 inhibitors

SGLT2 inhibitors reduce blood glucose by preventing reabsorption of glucose in the proximal tubule. They improve glycaemic control and induce weight loss.<sup>114</sup> Although safe and effective in patients with mild-to-moderately impaired renal function, their use is not recommended in haemodialysis.<sup>115–117</sup>

There is limited evidence available on the use of SGLT2 inhibitors for PTDM. It is important to note that they increase the risk for urinary tract infection.<sup>118</sup> A 2020 meta-analysis of 132 renal transplant recipients taking SGLT-2 inhibitors showed a significant reduction in body weight and HbA1c. There were no significant changes in eGFR. Fourteen patients in this study suffered urinary tract infections.<sup>119</sup>

It is important to that large trials such as the EMPA-REG OUTCOME trial<sup>120</sup> and the DAPA-CKD study<sup>121</sup> demonstrate that SGLT2 inhibitors are reno-protective independent of their ability to lower blood glucose. DAPA-CKD was a randomised controlled trial of dapagliflozin in 2152 participants with CKD. Primary outcomes were a composite score of sustained decline in eGFR of at least 50%, development or ESKF or death from renal or cardiovascular causes. Hazard ratio for development of the primary outcome with dapagliflozin compared with placebo was 0.61 (95% CI 0.51–0.72,  $p < 0.001$ ), with a number-needed-to-treat of 19 (95% CI 15–27). This benefit was similar for patients with and without type 2 diabetes.<sup>121</sup>

The mechanism by which dapagliflozin reduces renal and cardiovascular complications is not fully understood but is thought to occur *via* renal and extrarenal mechanisms. These include improving glycaemia, promotion of diuresis and natriuresis, blood pressure reduction and modulation of the sympathetic nervous and rennin-angiotensin-aldosterone systems.<sup>122</sup>

### Insulin therapy

As described in the previous section, there are limited therapeutic options for patients with diabetes and ESKF; therefore, these patients are frequently managed with insulin alone. As described in the section ‘Glucose homeostasis in CKD’, there is a reduction in insulin requirement in advanced CKD due to diminished renal clearance. Once the eGFR falls to 10 ml/min, insulin requirements fall to approximately 50%.<sup>123</sup> Patients with DM and CKD who are treated with insulin are at great risk of glycaemic variability and hypoglycaemia. It is thought that the safest regimen in ESKF is with basal bolus insulin and regular capillary blood glucose monitoring. A 25% reduction in the dose of basal bolus insulin on haemodialysis days is recommended to avoid hypoglycaemia.<sup>39</sup>

No randomised studies have been performed to investigate insulin regimens in PTDM. Early post-operative hyperglycaemia tends to be treated with once-daily Neutral protamine Hagedorn (NPH) insulin, which is titrated downwards as steroid doses are weaned. Longer-term, standard insulin regimens are used.

### Perspectives and directions for future research

The DIRECT trial was a randomised controlled comparing a primary care-led weight management programme, which included withdrawal of antidiabetic and antihypertensive medication, to best-practice care by guidelines. The primary outcomes were weight loss of at least 15 kg and remission of DM (HbA1c less than 6.5% after 2 months off all antidiabetic medications). The study recruited 306 participants. Diabetes remission was achieved in 46% of participants in the intervention group, compared with 4% of those in the control group (odds ratio 19.7, 95% CI 7.8–49.8,  $p < 0.0001$ ). The intervention group also had statistically significant improvements in quality of life.<sup>124</sup> Remissions were sustained at 24 months by more than a third of participants in the intervention group. Sustained remission was linked to sustained weight loss.<sup>125</sup> A further prospective cohort study of 468 renal transplant recipients demonstrated that a high Mediterranean Style Diet Score is associated with a lower risk of NODAT (hazard ratio 0.23, 95% CI 0.09–0.64,  $p = 0.004$ ) and all-cause mortality (hazard ratio 0.51, 95% CI 0.29–0.89,  $p = 0.02$ ) compared with a low Mediterranean Style Diet Score.<sup>126</sup>

Unfortunately, most nutritional studies are retrospective and observational. This is due to the complexities associated with performing nutritional randomised controlled trials. The DIRECT trial suggests there may be a role for nutritional intervention in patients on dialysis or post-transplant. There is a great need for interventional studies with adequate numbers of participants investigating the role of diet in patients with CKD and diabetes, and in the treatment and prevention of PTDM.

### Conclusion

Diabetes mellitus is a common cause of morbidity and mortality in end-stage kidney patients. End-stage kidney failure and renal replacement therapy affect glucose metabolism, glucose monitoring, pharmacokinetics and pharmacodynamics of agents used for treatment for diabetes. Hence, the management of diabetes is important in patients on dialysis and post kidney transplantation, and requires physician understanding of the nuances of treatment, to improve outcomes in these patients with high medication burden and poor quality of life.

### Author contributions

Dr Eyal Ben-David designed the manuscript and wrote and revised it

Dr Richard Hull designed the manuscript

Professor Debasish Banerjee designed, wrote and revised the manuscript

### Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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