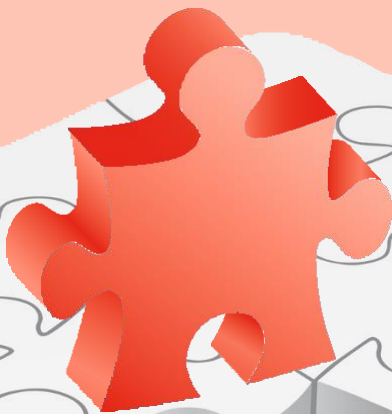


**JBDS-IP** Joint British  
Diabetes Societies  
for inpatient care

## Management of adults with diabetes on dialysis

March 2023



**DiABETES UK**  
CARE. CONNECT. CAMPAIGN.

**ABCD**  
Association of British Clinical Diabetologists

**DISN**  
UK GROUP

**UKKA**  
UK Kidney Association

**This document is coded JBDS 11 in the series of JBDS documents:**

**Other JBDS documents:**

<i>The hospital management of hypoglycaemia in adults with diabetes mellitus</i>	JBDS 01
<i>The management of diabetic ketoacidosis in adults</i>	JBDS 02
<i>Management of adults with diabetes undergoing surgery and elective procedures: improving standards</i>	JBDS 03
<i>Self-management of diabetes in hospital</i>	JBDS 04
<i>Glycaemic management during the inpatient enteral feeding of stroke patients with diabetes</i>	JBDS 05
<i>The management of the hyperosmolar hyperglycaemic state (HHS) in adults with diabetes</i>	JBDS 06
<i>Admissions avoidance and diabetes: guidance for clinical commissioning groups and clinical teams</i>	JBDS 07
<i>Management of hyperglycaemia and steroid (glucocorticoid) therapy</i>	JBDS 08
<i>The use of variable rate intravenous insulin infusion (VRIII) in medical inpatients</i>	JBDS 09
<i>Discharge planning for adult inpatients with diabetes</i>	JBDS 10
<i>Management of adults with diabetes on dialysis</i>	JBDS 11
<i>Managing diabetes and hyperglycaemia during labour and birth</i>	JBDS 12
<i>The management of diabetes in adults and children with psychiatric disorders in inpatient settings</i>	JBDS 13
<i>A good inpatient diabetes service</i>	JBDS 14
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<i>The management of glycaemic control in people with cancer</i>	JBDS 17
<i>Concise advice on Inpatient Diabetes (COVID Diabetes)</i>	JBDS 18

**These documents are available to download from the ABCD website at:**

<https://abcd.care/joint-british-diabetes-societies-jbds-inpatient-care-group> and the Diabetes UK website at [www.diabetes.org.uk/joint-british-diabetes-society](http://www.diabetes.org.uk/joint-british-diabetes-society)

**These guidelines can also be accessed via the [Diabetologists \(ABCD\)](#) app (need ABCD membership to access the app)**

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## **Statement for JBDS guidelines**

JBDS guidelines have been developed to advise on the care process for people with Diabetes currently under Hospital care.

The guideline recommendations have been developed and reviewed by a multidisciplinary team led by the Joint British Diabetes Society (JBDS) and including representation from Primary Care Diabetes Society and Diabetes UK. People with diabetes have been involved in the development of the guidelines via stakeholder events organised by Diabetes UK.

It is intended that the guideline will be useful to clinicians and service commissioners in planning, organising and delivering high quality diabetes care. There remains, however, an individual responsibility of healthcare professionals to make decisions appropriate to the circumstance of the individual, informed by them and/or their guardian or carer and taking full account of their medical condition and treatment.

When implementing this guideline full account should be taken of the local context and in line with statutory obligations required of the organisation and individual. No part of the guideline should be interpreted in a way that would knowingly put staff, those with diabetes or anyone else at risk.

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## **Disclaimer**

The information contained in this guidance is a consensus of the development and consultation groups' views on current treatment. It should be used in conjunction with any local policies/procedures/guidelines and should be approved for use according to the trust clinical governance process. Care has been taken in the preparation of the information contained in the guidance. Nevertheless, any person seeking to consult the guidance, apply its recommendations or use its content is expected to use independent, personal medical and/or clinical judgement in the context of the individual clinical circumstances, or to seek out the supervision of a qualified clinician. The group makes no representation or guarantee of any kind whatsoever regarding the guidance content or its use or application and disclaim any responsibility for its use or application in any way.

To enable the guideline to stay relevant, it is envisaged that all of the JBDS guidelines will be updated or reviewed each year. As such these are 'living' documents – designed to be updated based on recently published evidence or experience. Thus, feedback on any of the guidelines is welcomed. Please email [christine.jones@nuh.nhs.uk](mailto:christine.jones@nuh.nhs.uk) with any comments, suggestions or queries.

**Conflict of interest statement:** The authors declare no conflicts of interest

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# Introduction

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This is an update of the guideline commissioned by the Joint British Diabetes Societies in conjunction with the UK Kidney Association previously published in 2016. The updated guideline has been informed by experts in diabetes and nephrology; including senior clinicians, specialty nurses, dietitians, pharmacists and people with diabetes who have experienced end stage kidney disease (ESKD) treatment.

The aim of this updated guideline is to improve the standards of care for people with diabetes (including both people with type 1 and type 2 diabetes) who are treated with dialysis.

The number of people with diabetes and kidney disease is increasing in the UK and this is reflected by the increasing number of people on ESKD treatment. In some units in the UK, over 40% of the people on dialysis have diabetes. (1)

The guideline highlights the organisational difficulties that people with diabetes on dialysis experience and suggests the need for organisation of their care to be centred around the individual. We hope that this guideline will be of use to all healthcare professionals whose work brings them in contact with this very vulnerable group of individuals.

The target audience specifically includes:

- Clinical staff working on dialysis units (nephrologists, haemodialysis specialist nurses and healthcare assistants)
- Clinicians working in diabetes networks (diabetologists, diabetes specialist nurses)

- General practitioners, practice nurses and district nurses
- Podiatrists
- Dietitians involved in the care of patients on dialysis

The original 2016 guidelines were the first national guidelines covering issues relating to diabetes management for this complex group. In updating this guideline, we have expanded the remit to include people with diabetes on peritoneal dialysis, and we have also updated other sections. This includes a major revision on the section on glycaemic monitoring and glycaemic targeting which takes into account the significant technological advances that have been made in relation to glucose monitoring. The section on complications now includes subsections relating to diabetic ketoacidosis and eye complications.

The writing committee recognise that encouraging change in care for people with diabetes on dialysis requires more than a guideline document. It needs to be accompanied by practical advice on how best to implement guideline recommendations. In order to facilitate this, we have aligned this guideline to work that is being undertaken as part of the national kidney quality improvement programme (KQuIP) in this area and the Diabetes Care in Haemodialysis (DiH) programme.

## **DIABETES CARE IN HAEMODIALYSIS PROGRAMME**

The DiH group has been established as a multi-professional, multidisciplinary working group to support the implementation of the 2016 JBDS guidelines and most importantly to facilitate improvements in the care for people with diabetes on haemodialysis.

The strategy has been built around:

- 1) Agreement of standards to define care of people with diabetes on maintenance haemodialysis (mHDx).
- 2) Agreement on an audit tool to support implementation of the guidelines for staff.
- 3) Engagement with haemodialysis staff and people with diabetes – learning about and disseminating good practice.
- 4) Development of an educational programme for staff.



## **1) STANDARDS FOR CARE OF PEOPLE WITH DIABETES ON MAINTENANCE HAEMODIALYSIS (mHDx)**

It is recognised how difficult it has been for each haemodialysis unit to meet all the recommendations within 2016 guidelines and much easier for them work towards achieving a set of standards that encompass the most important elements.

Originally five standards were agreed through a consultative process and thereafter these were to be used to support commissioning arrangements for dialysis units and encourage improvements in care.

Following the update of this guideline the current standards will be reviewed and updated. The process for the delivery of any agreed standards will vary from site to site depending on service configurations. However responsibility for meeting these standards will ultimately lie with the service commissioners whilst the responsibility for recording achievement of standards rests with the dialysis unit service leads.

## **2) DEVELOPMENT OF AN AUDIT TOOL TO SUPPORT STAFF ACHIEVE STANDARDS**

To support the implementation of the standards, an appropriate audit tool was developed). This defines measures that allow units to demonstrate that they meet the standards and incorporated within the audit tool are examples of good practice in relation to that particular area and advice on collection of data. Following this updated guideline the audit tool will be refreshed to bring it in line with the current recommendations and standards.

## **3) ENGAGEMENT WITH STAFF AND PEOPLE WITH DIABETES TO SUPPORT THE DISSEMINATION OF GOOD PRACTICE**

There is a wealth of good practice being undertaken across the country and a programme of work will be undertaken to collate these examples. It is proposed that these examples will be linked to both the audit tool used by dialysis units to demonstrate good practice and also be held on the KQuIP website.

In conjunction with this element of the programme, a guide for people with diabetes who are on dialysis has been developed to help them appreciate the care that they should expect to receive. This will be aimed at empowering people with diabetes in relation to their understanding of their diabetes and its implications for their management whilst receiving

dialysis. It is proposed that the guide will be piloted and assessed using patient activation measures to demonstrate effectiveness.

#### **4) EDUCATIONAL PROGRAMME**

There is unlikely to be any change in the care delivered to people with diabetes on dialysis unless staff who work with these individuals attain some degree of knowledge and understanding of the key issues that are relevant to such people. To support this, an educational program has been developed which consists of a blended educational strategy. This includes face-to-face teaching which could be delivered on a single day or through a series of sessions. In addition to this, an e-learning programme has been developed that could be undertaken on an individual basis to augment learning from a face-to-face event or indeed undertaken as a stand-alone resource.

The face-to-face educational programme has been designed to encompass the main elements of this guideline. The educational programme will then be made available for use more widely with appropriate resources workbooks and materials available to be delivered. Alternatively, members of the faculty developing this program could be asked to influence local delivery on a regional basis.

#### **PEOPLE WITH DIABETES ON PERITONEAL DIALYSIS**

It is recognised that up until the production of this 2022 revision to the 2016 guidelines, much of the work of the DiH programme has been focused on people with diabetes on haemodialysis and that there now needs to be some focus also in relation to people who undertake peritoneal dialysis to ensure that they to achieve appropriate care. It is envisaged with production of this guideline the DiH working group will work with KQuIP to facilitate this.

#### **References for Introduction**

1. UK Renal Registry (2021) UK Renal Registry 23rd Annual Report – data to 31/12/2019, Bristol, UK. Available from [www.renal.org/audit-research/annual-report](http://www.renal.org/audit-research/annual-report)  
Accessed 09.02.23

# Methodology

## Search strategies

Authors of each section were asked to undertake a literature search using standard databases including PubMed, MEDLINE, Google Scholar, CINAHL and ClinicalTrials.gov, particularly focussing on newer articles from 2016 onwards. Searches were limited to publications in English.

## Evidence grading

In general, we followed the principles set out in the UK Kidney Association’s “Clinical Practice Guideline Development Manual” and grade “Recommendations for Use” and “Recommendations for Implementation” according to its two-tier grading system (Table 1.2). We use the term “recommend” within the guideline text where recommendations are based on Grade 1 evidence and prefer the term “suggest” for those based on Grade 2 evidence.

As described in the document there is very little data to support any recommendations in relation to the management of diabetes in people on peritoneal dialysis, and we have defined these recommendations as “practice points”.

**Table 1.2: UK Kidney Association’s grading system for recommendations’ strength and evidence quality**

Level of evidence	Evidence quality
<ul style="list-style-type: none"><li>• Grade 1 recommendation is a strong recommendation to do (or not do) something, where the benefits clearly outweigh the risks (or vice versa) for most, if not all patients (i.e. recommendations)</li><li>• Grade 2 recommendation is a weaker recommendation, where the risks and benefits are more closely balanced or are more uncertain (i.e. suggestions)</li></ul>	<ul style="list-style-type: none"><li>• Grade A evidence means high-quality evidence that comes from consistent results from well-performed randomized controlled trials, or overwhelming evidence of some other sort.</li><li>• Grade B evidence means moderate-quality evidence from randomized trials that suffer from serious flaws in conduct, inconsistency, indirectness, imprecise estimates, reporting bias, or some combination of these limitations, or from other study designs with special strength.</li><li>• Grade C evidence means low-quality evidence from observational studies, or from controlled trials with several very serious limitations.</li><li>• Grade D evidence is based only on case studies or expert opinion.</li></ul>

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*With special thanks to Christine Jones for her administrative work and help with these  
guidelines and with JBDS-IP*

# List of Abbreviations

ACEI	Angiotensin convertase inhibitor
ARB	Angiotensin 2 receptor blockade
AGP	Ambulatory glucose profile
APD	Automated peritoneal dialysis
BCVA	Best central visual acuity
BMI	Body mass index
CAPD	Continuous ambulatory peritoneal dialysis
CBG	Capillary blood glucose
CGM	Continuous glucose monitoring
CKD	Chronic kidney disease
CRT	Central retinal thickness
CSII	Continuous subcutaneous insulin infusion
CV	Coefficient of variation
CVD	Cardiovascular disease
DiH	Diabetes Care in Haemodialysis programme.
DKA	Diabetic ketoacidosis
DME	Diabetic macular oedema
DPP-4	Dipeptidyl-peptidase-4
DR	Diabetic retinopathy
DSN	Diabetes specialist nurse
EPO	Erythropoietin
ESKD	End stage kidney disease
Flash GM	Flash glucose monitoring
FPG	Fasting plasma glucose
FRII	Fixed rate insulin infusion
GA	Glycated albumin
GDH-PQQ	Glucose dehydrogenase pyrroloquinoline quinone
GI	Glycaemic index
GO	Glucose oxidase
GV	Glycaemic variability
Hb	Haemoglobin
HbA <sub>1c</sub>	Glycated haemoglobin
HCPs	Health care professionals
IBW	Ideal body weight
IDFG	Inter dialysis fluid gains
IDWG	Inter dialysis weight gain
IM	Intramuscular
IQR	Interquartile range
KQuIP	Kidney quality improvement programme
MAGE	Mean amplitude of glucose excursion
MDI	Multiple daily injections
mHDx	Maintenance haemodialysis
MODD	Mean of daily differences
NPH	Neutral protamine Hagedorn
OAD	Oral antidiabetic drugs
OCT	Optical coherence tomography
OGTT	Oral glucose tolerance test
PAD	Peripheral arterial disease
PD	Peritoneal dialysis
PDR	Proliferative diabetic retinopathy
PEW	Protein energy wasting

RAS	Renin–angiotensin system
RBC	Red blood cell
RCT	Randomised controlled trials
SGLT2I	Sodium -glucose cotransporter 2 inhibitor
SMBG	Self-monitoring of blood glucose
SU	Sulfonylureas
TIR	Time in range
T1D	Type 1 diabetes
T2D	Type 2 diabetes
TZD	Thiazolidinedione
UF	Ultrafiltration
VEGF	Vascular endothelial growth factor
VH	Vitreous haemorrhage



# Summary of all recommendations

## RECOMMENDATIONS FOR ORGANISATION OF CARE (SECTION 1)

1.1. It is recommended that all people with diabetes undergoing either haemodialysis or peritoneal dialysis should have a documented annual review of their diabetes which includes foot and eye screening through the primary care diabetes register. The responsibility for coordinating this rests with the primary care, diabetes or nephrological service caring for the person. In order to ensure that this is effectively undertaken:

- a) The assessment should be coordinated in a manner that recognises that the person on haemodialysis is usually attending the dialysis unit three times per week.
- b) The information pertaining to the review should be available to all healthcare staff involved in the care of the individual.
- c) Each person undertaking in-centre haemodialysis should have a named link worker on the dialysis unit who can ensure that the assessments have been undertaken and have been acted upon. *(Grade 1B)*

1.2. It is recommended that all people with diabetes undergoing maintenance haemodialysis or on a peritoneal dialysis programme should have access to a named Diabetes Specialist Nurse (DSN) responsible for providing support in relation to ongoing care of diabetes and its complications. Where commissioned, the DSN would be able to provide rounds on the haemodialysis unit and outpatient clinics for those on peritoneal dialysis, offering patient education and clinical advice where necessary. A link nurse on the haemodialysis unit will be expected to coordinate regular foot checks, blood glucose monitoring training and injection technique. This could be a healthcare assistant or a registered nurse following appropriate training and competency assessment. The link nurse would be expected to escalate foot problems for specialist foot assessment and on-going referral to the specialist foot team. *(Grade 1D)*

1.3. It is recommended that a process to coordinate the management of acute metabolic, eye, cardiovascular and/or foot emergencies should be established with

effective communication between the dialysis (haemodialysis or peritoneal) unit, the specialist diabetes team and primary care. (*Grade 1C*)

1.4 It is recommended that all people with diabetes on dialysis with acute and/or chronic glycaemic instability, or on insulin therapy should have specialist diabetes input. (*Grade 1C*).

## **RECOMMENDATIONS FOR GLYCAEMIC ASSESSMENT IN PEOPLE WITH DIABETES ON DIALYSIS (SECTION 2)**

2.1 We suggest that glycated haemoglobin (HbA<sub>1c</sub>) should be used with caution in people with diabetes on dialysis, as it may not provide a true reflection of prevailing glucose control, and clinicians should be aware of its deficiencies. In particular, HbA<sub>1c</sub> does not give a good reflection of glycaemic variability (GV) and may not adequately identify people who are at high risk of hypoglycaemia. (*Grade 2C*)

2.2 We suggest that HbA<sub>1c</sub> > 80 mmol/mol (9.5%) is likely to reflect poor glycaemic control, unless there is severe iron deficiency. (*Grade 2C*)

2.3 We suggest that there is inadequate data on the use of alternative glycated proteins such as glycated albumin (GA) or fructosamine for monitoring glucose control in people with diabetes on dialysis, although use of GA should be explored in further research. (*Grade 2C*)

2.4 We suggest that for people with diabetes on dialysis, direct glucose estimations (self-monitoring of blood glucose [SMBG]) should routinely be offered. Intermittently scanned (Flash) glucose monitoring or continuous glucose monitoring [CGM]) should also be considered for the assessment of glucose control. (*Grade 2C*)

2.5 We recommend that all people with diabetes on dialysis treated with insulin and/or sulfonylureas must have access to SMBG. (*Grade 1C*)

2.6 We suggest that healthcare professionals (HCPs) involved in adjusting diabetes therapy should review meter downloads and any point of care SMBG data at every diabetes related visit to optimise treatment, assess variability and hypoglycaemia risk. (*Grade 2C*)

2.7 We recommend that glucose meters using Glucose oxidase [GO] or Glucose dehydrogenase pyrroloquinoline quinone [GDH-PQQ] enzymatic methods for glucose assessment should not be used in people with diabetes on dialysis. (*Grade 1B*)

**2.8** We recommend that people with diabetes on dialysis meeting national criteria for intermittently scanned continuous glucose monitoring should be offered this option and receive training and support for its optimal use. (*Grade 1C*)

**2.9** We suggest that all people with diabetes on dialysis using insulin who have recurrent hypoglycaemia or loss of hypoglycaemia awareness should be offered real-time CGM. (*Grade 2C*)

**2.10** We suggest that long term CGM should be considered in people with diabetes on dialysis who are treated with insulin and/or sulfonylurea, unless practical issues make long-term use difficult, in which case 6 to 12 monthly diagnostic CGM can be used to aid dose adjustments and adequacy of treatment. (*Grade 2C*)

**2.11** We suggest that people with diabetes on dialysis not eligible for intermittently scanned (Flash) glucose monitoring should be considered for regular diagnostic (6-12 monthly) CGM if their SMBG results show frequent (>5%) glucose readings below 4 mmol/L, frequent (>20%) glucose readings above 14 mmol/L, if they are unable to undertake SMBG twice a daily for 1-2 weeks periods, or if they have HbA<sub>1c</sub> < 42 mmol/mol (6.0%) or > 80 mmol/mol (9.5%). (*Grade 2C*)

## **RECOMMENDATIONS FOR NON-INSULIN GLUCOSE LOWERING THERAPIES (SECTION 3A)**

**3A.1** Sulfonylureas, Glinides, Acarbose, Metformin and Sodium Glucose Transporter-2 inhibitors (SGLT-2Is) are not licensed for use in patients on dialysis. We therefore do not recommend their use in people with diabetes on dialysis. (*Grade 1B*)

**3A.2** Pioglitazone is not licensed for use in patients on dialysis although it is licenced for use in patients with eGFR down to 4 mL/min and has been used safely in patients on maintenance haemodialysis [mHDx]. We therefore suggest its use with caution in people with diabetes on mHDx. (*Grade 1C*)

**3A.3** The DPP-4 inhibitors linagliptin, sitagliptin, vildagliptin and alogliptin are all licenced for use in patients on dialysis. We therefore recommend their use in people with diabetes on dialysis. Dose reductions for sitagliptin, vildagliptin and alogliptin are required. (*Grade 1B*)

**3A.4** GLP1-receptor agonists are not licenced for use in patients with eGFR of <15 mL/min but have been used safely in patients on mHDx. We therefore suggest their use with caution in people with diabetes on mHDx (*Grade 2D*)

## **RECOMMENDATIONS FOR INSULIN THERAPY IN PEOPLE WITH DIABETES ON DIALYSIS (SECTION 3B)**

**3B.1** The aim of insulin therapy in people with diabetes on dialysis is to improve quality of life and avoid extremes of hypo- and hyperglycaemia. *(Grade 2C)*

**3B.2** We suggest that health care professionals (HCPs) involved in adjusting diabetes therapy review meter downloads and any point of care self-monitoring of blood glucose (SMBG) data at every diabetes related visit to optimise insulin treatment, assess variability and hypoglycaemia risk. *(Grade 2C)*

**3B.3** We suggest that HCPs should consider periodic (1-2x per year) “diagnostic” continuous glucose monitoring (CGM) analysis for all people with diabetes on dialysis on insulin treatment in order to guide future treatment planning unless they are already using Flash glucose monitoring (Flash GM) or real-time CGM systems. *(Grade 2C)*

**3B.4** We suggest that basal bolus regimes may be most flexible and best suited to the glycaemic variability (GV) seen in people with diabetes on dialysis. *(Grade 2C)*

**3B.5** We suggest that a reduction in insulin doses by 25% on haemodialysis days may reduce risk of hypoglycaemia, but assessment with CGM may offer a better guide to insulin dosing on dialysis and non-dialysis days. *(Grade 2C)*

**3B.6** We suggest that in people with diabetes on dialysis who are unable to manage a basal bolus regimen, consideration should be given to once daily regimes with longer acting insulin. *(Grade 2C)*

**3Bb.7** We suggest that if patients have troublesome hypoglycaemia on NPH insulin, conversion to analogue insulin may be considered. *(Grade 2C)*

## **RECOMMENDATIONS FOR DIETARY INTERVENTIONS FOR PEOPLE WITH DIABETES ON DIALYSIS (SECTION 4)**

**4.1** We recommend that the type of diabetes should be identified, and personalized dietary goals should be agreed that supports both the diabetes and renal aspects of the diet. *(Grade 1C)*

**4.2** We recommend that each haemodialysis unit should have access to appropriate dietary expertise able to provide a holistic approach to the individual with diabetes. *(Grade 1D)*

- 4.3 We suggest that total energy should come from 50–60% carbohydrate, <30% fat and at least 15% from protein. *(Grade 2D)*
- 4.4 We recommend that individuals on maintenance haemodialysis [mHDx] achieve an energy intake of 30–40 kcal/kg ideal body weight (IBW). *(Grade 1D)*
- 4.5 We recommend that individuals on mHDx achieve a protein intake of >1.0 g/kg IBW. *(Grade 1C)*
- 4.6 We recommend that for people on mHDx with diabetes, dietary advice should be given for both dialysis and non-dialysis days to minimise significant glycaemic and caloric excursions. *(Grade 1D)*
- 4.7 We recommend that low potassium dietary restrictions are not required unless serum potassium is persistently  $\geq 6.0$  mmol/L predialysis. *(Grade 1D)*
- 4.8 We recommend that foods containing phosphate additives which have low nutrient value should be targeted prior to other high phosphate foods e.g. wholegrain products and foods with high biological value protein. *(Grade 1D)*
- 4.9 We recommend that clinicians should ensure that individuals on maintenance haemodialysis with diabetes are aware that they are more likely to be able to maintain inter-dialytic fluid gain (IDFG) at <4.5% of dry weight or <2 kg if they optimise their glucose control. *(Grade 1D)*
- 4.10 We recommend a salt intake of <5 g/day for people with diabetes on dialysis. *(Grade 1C)*
- 4.11 We recommend that all individuals with diabetes on dialysis should be screened for protein energy wasting (PEW) using a valid nutritional screening tool. *(Grade 1C)*
- 4.12 We recommend that initiation of nutrition support should be considered in those at risk of PEW; the indicators are the same in those with and without diabetes. *(Grade 1C)*
- 4.13 We recommend that individuals should receive dietary counselling and oral nutrition support as their first-line treatment if unable to meet their nutritional needs orally. Enteral or parenteral nutrition may need consideration if these interventions are insufficient. *(Grade 1D)*
- 4.14 We recommend that individuals with gastroparesis should be encouraged to have frequent small meals that are low in fat and fibre to help manage the condition. *(Grade 1C)*

4.15 We recommend that individuals who are being considered for a kidney transplant who are overweight/obese should be encouraged to lose weight through dietary counselling on a calorie restrictive diet, making sure protein requirements are met (1.0 g/kg IBW). *(Grade 1B)*

4.16 We recommend that dietary counselling should also ideally include behavioural change strategies and increased physical activity. *(Grade 1B)*

4.17 We recommend that all individuals with an elevated body mass index (BMI) who may not be considered for transplantation if unable to lose weight through diet, exercise and behavioural change should be considered for weight-reducing strategies including bariatric surgery. *(Grade 1C)*

4.18 We recommend that individuals on peritoneal dialysis (PD) achieve an energy intake of 30-35kcal/kg IBW. *(Grade 1D)*

4.19 We recommend that individuals on PD achieve a minimum protein intake of 1.0-1.2g/kg IBW. *(Grade 1C)*

4.20 We recommend that calories provided through PD solutions should be estimated with caution. *(Grade 1D)*

## **RECOMMENDATIONS FOR MANAGEMENT OF HYPOGLYCAEMIA IN PEOPLE WITH DIABETES ON DIALYSIS (SECTION 5A)**

### **For people on active treatment of diabetes with insulin:**

5A.1 We recommend that where there is a pre-dialysis glucose of <7 mmol/L, 20–30 g low glycaemic index carbohydrate is provided at the beginning of the haemodialysis session to prevent further decline of blood glucose level. *(Grade 1D)*

5A.2 We recommend that capillary glucose should be assessed pre- and post-haemodialysis. *(Grade 1D)*

5A.3 We suggest that the dialysis unit should ensure a hypoglycaemia treatment is always accessible to patients, including during travelling to and from the dialysis unit. *(Grade 2D)*

### **In cases of hypoglycaemia**

5A.4 We recommend that an appropriate rapid-acting carbohydrate treatment should be provided to take into account fluid, potassium and phosphate restrictions. *(Grade 1D)*

5A.5 After treatment initiation, glucose level should be checked 15 minutes after the treatment is given. If not above 4 mmol/L, a repeat dose of the 15 g rapid glucose

followed by 10–20 g complex or low glycaemic index carbohydrate is recommended. *(Grade 1C)*

5A.6 We recommend that patients and staff should be educated in regard to the appropriate treatment of mild to moderate hypoglycaemia and hypoglycaemia unawareness. *(Grade 1D)*

### **RECOMMENDATIONS FOR FOOTCARE (SECTION 5B)**

5B.1 We recommend that all people with diabetes on dialysis should be considered high risk of developing foot ulcers and are at high risk of amputation. *(Grade 1B)*

5B.2 We recommend that all people with diabetes on dialysis should inspect their feet daily and if they are unable to do this because of poor eyesight or frailty their carers should be advised to undertake this for them. *(Grade 1C)*

5B.3 We recommend that the heels of all people with diabetes on maintenance haemodialysis [mHDx] should be protected with a suitable pressure relieving device during haemodialysis. *(Grade 1C)*

5B.4 We recommend that all people with diabetes on dialysis should have regular podiatry review. *(Grade 1C)*

5B.5 We recommend that all people with diabetes on dialysis should have their feet screened monthly using a locally agreed tool and by competent staff on the dialysis unit. *(Grade 1C)*

5B.6 We recommend that if the individual has an ulcer or there is any other concern the patient should be referred to the diabetic foot team within one working day and each dialysis unit should ensure that there is a clearly defined escalation pathway for these individuals. *(Grade 1B)*

5B.7 If the individual is on home dialysis, we suggest it is the responsibility of the clinician in charge of their care to ensure that they have an annual foot review and are attending review by the foot protection team. *(Grade 2B)*

5B.8 We recommend that any individual presenting with a hot swollen foot should be referred to the diabetic foot team within 24 hours. *(Grade 1B)*

### **RECOMMENDATIONS FOR RETINOPATHY IN PEOPLE WITH DIABETES ON DIALYSIS (SECTION 5C)**

5C.1 We recommend that all people with diabetes on dialysis should be asked about when they last had retinal screening as part of their annual review. Ideally, this

should have occurred within six months prior to starting dialysis in order to ensure that those who have severe non proliferative retinopathy, proliferative retinopathy or macular oedema have been referred for treatment ideally before initiating dialysis.

*(Grade 1C)*

**5C.2** We recommend the implementation of the UK Kidney Association guidelines on management of glycaemia, hypertension, lipids and anaemia in people with diabetes on dialysis in order to reduce the risk of progression of retinopathy after starting dialysis. *(Grade 1C)*

**5C.3** We suggest that in those individuals identified as having severe macular or retinal disease extra care is taken to minimise intradialytic hypotension and rapid change in BP or fluid status during haemodialysis. *(Grade 2D)*

**5C.4** We recommend continuing with anti-coagulation and anti-platelets therapies when indicated in patients with diabetic retinopathy on dialysis. *(Grade 1C)*

**5C.5** We recommend prompt control of hypertension in patients with diabetic retinopathy on dialysis following initiation or maximisation of erythropoietin therapy. *(Grade 1C)*

**5C.6** We suggest the use of angiotensin convertase inhibitors (ACEIs) and angiotensin 2 receptor blocker (ARBs) to treat hypertension in patients with diabetic retinopathy on dialysis. *(Grade 2B)*

**5C.7** We recommend that if people with diabetes on dialysis experience acute changes to their vision, they should be referred urgently to a hospital eye service for an urgent assessment and that each dialysis unit should have an escalation pathway for such individuals. *(Grade 1B)*

## **RECOMMENDATIONS FOR DIABETIC KETOACIDOSIS IN PEOPLE ON DIALYSIS (SECTION 5D)**

### **Recognising Diabetic Ketoacidosis (DKA) on the haemodialysis unit**

**5D.1** We suggest that every haemodialysis unit should have point of care blood ketone testing available and staff should be trained in its use. *(Grade 2D)*

**5D.2** People with diabetes on maintenance haemodialysis [mHDx] should have their blood ketones checked using point of care testing kits if they have:

- Type 2 diabetes (T2D) and their pre-dialysis or post-dialysis capillary blood glucose (CBG) is persistently raised above 15.0 mmol/L (2



consecutive readings taken an hour apart) and they have symptoms suggestive of DKA OR

- Type 1 diabetes (T1D) and have CBG above 15.0 mmol/L. (See Table 1.1 for when to test for ketones) (*Grade 2D*).

**5D.3** If blood ketones are above 3.0 mmol/L, the person should have access to personnel and facilities to enable rapid and appropriate assessment and management of DKA. (*Grade 2D*)

**5D.4** We suggest there should be a pathway in place at each haemodialysis unit for the rapid and safe prescription and administration of a bolus dose of insulin for use in an emergency. (*Grade 2D*)

**5D.5** If there is a delay in transfer to a facility for intravenous insulin infusion, we suggest the following (*Grade 2C*):

- a) Administration of subcutaneous bolus dose of short acting insulin at a dose of 0.05units/kg
- b) Hourly monitoring of CBG and blood ketones
- c) Clear documentation of the administered dose and timing of insulin bolus and handing this information over to the receiving team when the patient is transferred.

### **Diagnosing Diabetic Ketoacidosis**

**5D.6** We suggest that the diagnostic criteria for DKA in people with ESKD are the same as for adults with preserved renal function (See Table 1.2). (*Grade 2C*)

### **Managing Diabetic Ketoacidosis**

**5D.7** After DKA has been diagnosed, treatment should follow the JBDS DKA Guidelines update June 2021 (See Table 1.3), paying particular attention to the fluid replacement regimen recommended for those on dialysis. (*Grade 2D*)

## **RECOMMENDATIONS FOR END OF LIFE CARE IN PEOPLE WITH DIABETES ON DIALYSIS (SECTION 5E)**

**5E.1** People with diabetes on dialysis approaching end of life or where a palliative care pathway has been agreed should be managed in accordance with Trend Diabetes End of Life clinical care recommendations for people with diabetes. Treatment and interventions should be focussed on symptoms. (*Grade 1D*)

**PRACTICE POINTS: MANAGEMENT OF DIABETES IN PEOPLE UNDERGOING PERITONEAL DIALYSIS – CLINICAL CONSIDERATIONS AND PRACTICE POINTS (SECTION 6)**

- 6.1 HbA<sub>1c</sub>, despite its limitations in persons with renal disease, is currently recommended as the preferred marker to assess long term glycaemic control in people with diabetes on PD.**
- 6.2 Other markers such as GA or fructosamine may be less reliable than HbA<sub>1c</sub> in PD.**
- 6.3 HbA<sub>1c</sub> treatment goals and targets should be individualized and other clinical parameters such as anaemia, erythropoietin treatment and PD regime have to be considered when managing diabetes in people on PD.**
- 6.4 Avoid the use of GDH-PQQ based glucometers or strips as these can give rise to falsely elevated BG readings in people undergoing PD with iodextrin. This can result in the risk of excessive insulin treatment and iatrogenic hypoglycaemia.**
- 6.5 An individualised approach with consideration of risks of hypoglycaemia, type of PD and glucose content of dialysate is required.**
- 6.6 Specialist input of the multidisciplinary diabetes team is required for high-risk people with diabetes on PD such as people with T1D, people on insulin with risk of hypoglycaemia, people with high glycaemic variability, people with recent hospital admissions with hypo/hyperglycaemic emergencies and people who have not received structured diabetes education within the last one year. (see Section 2)**
- 6.7 All people with diabetes on PD should receive education on the risk of hypoglycaemia, advice on mitigating risks and guidance on self-management**
- 6.8 For people with diabetes on PD requiring insulin treatment we advise the use of insulin subcutaneously only.**
- 6.9 We do not recommend intraperitoneal administration of insulin due to the lack of efficacy data and the known risks.**
- 6.10 If using glucose-based dialysates there may be a need for increased insulin doses to counter the systemic absorption of glucose from the dialysate.**
- 6.11 Exact insulin titrations and regimens should be individualized. A standard MDI or CSII (in T1D) may be preferred as it gives more flexibility towards dose titrations.**

## **SECTION 1 ORGANISATION OF CARE**

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### **RECOMMENDATIONS FOR SECTION 1**

**1.1. It is recommended that all people with diabetes undergoing either haemodialysis or peritoneal dialysis should have a documented annual review of their diabetes which includes foot and eye screening through the primary care diabetes register. The responsibility for coordinating this rests with the primary care, diabetes or nephrological service caring for the person. In order to ensure that this is effectively undertaken:**

- a) The assessment should be coordinated in a manner that recognises that the person on haemodialysis is usually attending the dialysis unit three times per week.**
- b) The information pertaining to the review should be available to all healthcare staff involved in the care of the individual.**
- c) Each person undertaking in-centre haemodialysis should have a named link worker on the dialysis unit who can ensure that the assessments have been undertaken and have been acted upon. (Grade 1B)**

**1.2. It is recommended that all people with diabetes undergoing maintenance haemodialysis or on a peritoneal dialysis programme should have access to a named Diabetes Specialist Nurse (DSN) responsible for providing support in relation to ongoing care of diabetes and its complications. Where commissioned, the DSN would be able to provide rounds on the haemodialysis unit and outpatient clinics for those on peritoneal dialysis, offering patient education and clinical advice where necessary. A link nurse on the haemodialysis unit will be expected to coordinate regular foot checks, blood glucose monitoring training and injection technique. This could be a healthcare assistant or a registered nurse following appropriate training and competency assessment. The link nurse would be expected to escalate foot problems for specialist foot assessment and on-going referral to the specialist foot team. (Grade 1D)**

**1.3. It is recommended that a process to coordinate the management of acute metabolic, eye, cardiovascular and/or foot emergencies should be established with**

effective communication between the dialysis (haemodialysis or peritoneal) unit, the specialist diabetes team and primary care. (Grade 1C)

1.4 It is recommended that all people with diabetes on dialysis with acute and/or chronic glycaemic instability, or on insulin therapy should have specialist diabetes input. (Grade 1C).

Over 68,000 adult individuals were receiving treatment for end stage kidney disease (ESKD) in the UK at the end of 2019, an increase of 2.5% from 2018.<sup>1</sup> The median age of individuals on ESKD treatment was 59.6 years and 61% were male. Diabetes is the most common identified primary renal condition accounting for 30.4% of people commencing dialysis.<sup>1</sup> The leading cause of death in those undertaking dialysis in the under 65 year old age group is cardiac disease and in people over 65, treatment withdrawal.<sup>1</sup> Figure 1.1 shows modalities of ESKD treatment in England and Wales at the end of 2019.

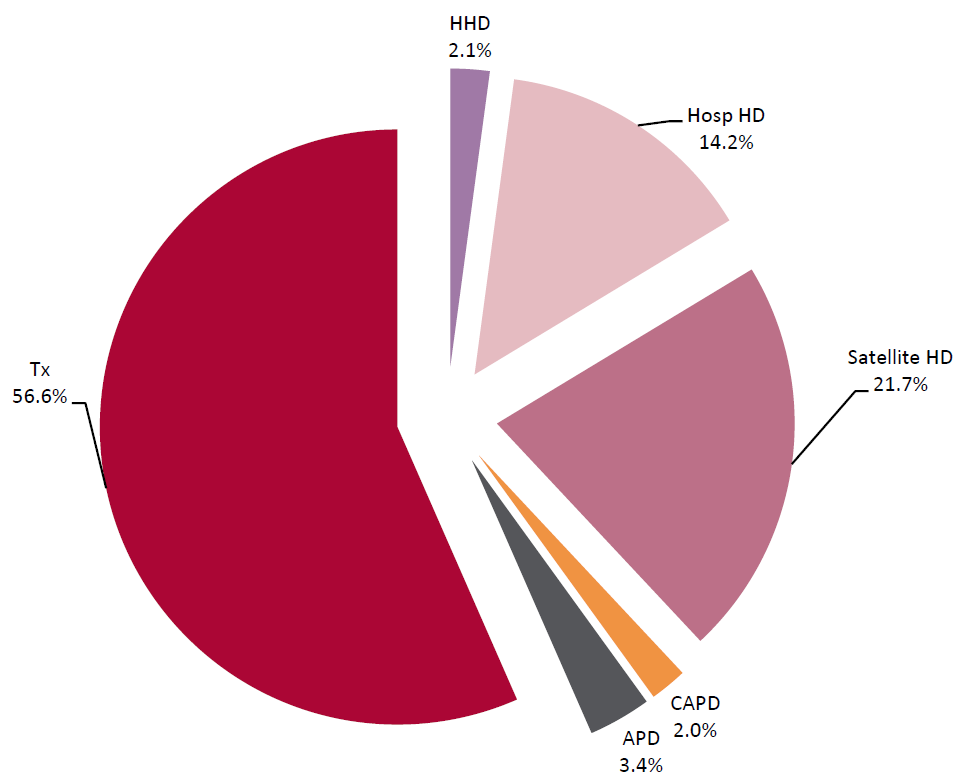


Figure 1.1 Treatment modality of adult patients prevalent to ESKD treatment on 31/12/2019 (HHD Home haemodialysis, Tx Transplant, CAPD continuous peritoneal dialysis, APD Automated peritoneal dialysis)

There are 70 units providing dialysis in the UK, including NHS organisations and satellite centres. Care may be provided in a tertiary centre, or in satellite units overseen by specialist services. Wherever care is delivered, there should be equality of access to specialist services and high quality of care.

In 2016, JBDS recommendations were developed for the care of people with diabetes who attend for haemodialysis.<sup>2</sup> However, fragmentation of services means that not all individuals with diabetes on haemodialysis receive the recommended care provision. People with diabetes on haemodialysis may have fragmented care, which may lead to many aspects of their care being overlooked, with renal, diabetes and primary care physicians all assuming that these needs are being met elsewhere.<sup>3</sup>

The management of people with diabetes on dialysis is complex, with a strong requirement for effective multidisciplinary care. Ideally, such patients should be reviewed in clinics that combine both diabetes and dialysis expertise, but attendance rates may be low as the individuals with diabetes on dialysis may not be keen to attend yet more hospital visits.<sup>2</sup> Low attendance rates may also be due to the fact that many of these individuals are older, frail, and socially deprived, with lives dominated by their dialysis schedule. People on home dialysis attend hospital much less often compared to those on in-centre based treatment; however, their diabetes care will still need to be provided in the community setting.

Diabetes specialist nurses (DSN) in the community and in the hospital setting are in a position to play a vital role in coordinating care and signposting individuals with diabetes for urgent care for eye, foot or acute metabolic complications. In addition, there is an important role for DSNs to support, educate, and empower people with diabetes on dialysis and their carers. There are very few DSNs with a specific remit for care for people with diabetes on dialysis, but where they exist, their impact can be profound in helping to organise care, and educate staff involved in dialysis care.

Local integrated care systems and acute trust hospitals should take into consideration that in-reach visits during dialysis unit attendance by diabetes service teams might be the most viable option to carry out regular diabetes review (e.g. annual review). To support this healthcare resources should be ringfenced and allocated accordingly.

## References for Section 1

2. UK Renal Registry (2021) UK Renal Registry 23rd Annual Report – data to 31/12/2019, Bristol, UK. Available from [www.renal.org/audit-research/annual-report](http://www.renal.org/audit-research/annual-report)  
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3. Kuverji A, James J, Gregory R, Frankel A, Burton JO A regional quality improvement project to improve the standards of care for people with diabetes who are on maintenance haemodialysis. *Future Health J* 2020 Feb (Suppl 1) s45-s46 PMID 32455280

## **SECTION 2 GLYCAEMIC ASSESSMENT IN PEOPLE WITH DIABETES ON DIALYSIS**

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## **RECOMMENDATIONS FOR SECTION 2**

**2.1 We suggest that glycated haemoglobin (HbA<sub>1c</sub>) should be used with caution in people with diabetes on dialysis, as it may not provide a true reflection of prevailing glucose control, and clinicians should be aware of its deficiencies. In particular, HbA<sub>1c</sub> does not give a good reflection of glycaemic variability (GV) and may not adequately identify people who are at high risk of hypoglycaemia. (Grade 2C)**

**2.2 We suggest that HbA<sub>1c</sub> > 80 mmol/mol (9.5%) is likely to reflect poor glycaemic control, unless there is severe iron deficiency. (Grade 2C)**

**2.3 We suggest that there is inadequate data on the use of alternative glycated proteins such as glycated albumin (GA) or fructosamine for monitoring glucose control in people with diabetes on dialysis, although use of GA should be explored in further research. (Grade 2C)**

**2.4 We suggest that for people with diabetes on dialysis, direct glucose estimations (self-monitoring of blood glucose [SMBG]) should routinely be offered. Intermittently scanned (Flash) glucose monitoring or continuous glucose monitoring [CGM]) should also be considered for the assessment of glucose control. (Grade 2C)**

**2.5 We recommend that all people with diabetes on dialysis treated with insulin and/or sulfonylureas must have access to SMBG. (Grade 1C)**

**2.6 We suggest that healthcare professionals (HCPs) involved in adjusting diabetes therapy should review meter downloads and any point of care SMBG data at every diabetes related visit to optimise treatment, assess variability and hypoglycaemia risk. (Grade 2C)**

**2.7 We recommend that glucose meters using Glucose oxidase [GO] or Glucose dehydrogenase pyrroloquinoline quinone [GDH-PQQ] enzymatic methods for glucose assessment should not be used in people with diabetes on dialysis. (Grade 1B)**

**2.8** We recommend that people with diabetes on dialysis meeting national criteria for intermittently scanned continuous glucose monitoring should be offered this option and receive training and support for its optimal use. *(Grade 1C)*

**2.9** We suggest that all people with diabetes on dialysis using insulin who have recurrent hypoglycaemia or loss of hypoglycaemia awareness should be offered real-time CGM. *(Grade 2C)*

**2.10** We suggest that long term CGM should be considered in people with diabetes on dialysis who are treated with insulin and/or sulfonylurea, unless practical issues make long-term use difficult, in which case 6 to 12 monthly diagnostic CGM can be used to aid dose adjustments and adequacy of treatment. *(Grade 2C)*

**2.11** We suggest that people with diabetes on dialysis not eligible for intermittently scanned (Flash) glucose monitoring should be considered for regular diagnostic (6-12 monthly) CGM if their SMBG results show frequent (>5%) glucose readings below 4 mmol/L, frequent (>20%) glucose readings above 14 mmol/L, if they are unable to undertake SMBG twice a daily for 1-2 weeks periods, or if they have HbA<sub>1c</sub> < 42 mmol/mol (6.0%) or > 80 mmol/mol (9.5%). *(Grade 2C)*

## **AUDIT STANDARDS FOR SECTION 2**

**2.1** Greater than 70% of people with diabetes on dialysis have undergone an appropriate assessment of glycaemic control over the last six months.

**2.2** Greater than 70% of people with diabetes on dialysis who are high risk for hypoglycaemia and GV, who have undergone Flash GM or CGM.



## 2.1 What's new?

This section has been significantly changed from the previous 2016 guideline due to the growing recognition that glycated proteins do not adequately reflect glycaemic control in people with diabetes on dialysis. The main change in this section is the suggestion for use of intermittently scanned or continuous glucose monitoring (CGM) in people with diabetes on dialysis who are at high risk of hypoglycaemia or glucose variability (GV).

References were identified through searches of PubMed for articles published using the terms “dialysis”, “haemodialysis”, “renal replacement therapy” and “peritoneal dialysis” in combination with the terms “glucose control”, “glycaemic monitoring”, “continuous glucose monitor” and “diabetes”. Relevant articles were identified through searches in the authors’ personal files. Articles resulting from these searches and relevant references cited in those articles were reviewed. Articles published in English were included. Findings from unpublished and on-going research work conducted by the authors and abstract presentations from conferences were discussed and cited as unpublished findings or with relevant abstract details.

## 2.2 Introduction

People with diabetes on dialysis have an increased risk of mortality and morbidity compared to people without diabetes on dialysis.<sup>1</sup> The reasons for this may be multifactorial. Whilst there is good evidence to suggest that tight glycaemic control reduces microvascular complications of diabetes,<sup>2-4</sup> the same level of evidence is not available for the management of glucose in people with diabetes on dialysis. There is, however, a danger of “therapeutic nihilism” when it comes to treating glucose in people with diabetes on dialysis, and glucose management can become neglected as such individuals contend with multiple health issues.<sup>5</sup>

The Association of British Clinical Diabetologists (ABCD) document, “Standards of Care for Glycaemic Assessment in People with Diabetes on Haemodialysis”,<sup>6</sup> recognised that current methods of assessing glycaemic control have limitations, and whilst the measurement of glycated haemoglobin (HbA<sub>1c</sub>) has been the mainstay for assessment of glycaemic control, this section highlights the difficulties of relying on HbA<sub>1c</sub> to monitor glucose in people with diabetes on dialysis.

Dynamic measures of glucose control can help individualise therapy and be used to identify high-risk people who would benefit from specialist diabetes input. This section will consider a

range of diabetes technologies that are available to monitor glycaemic control in people with diabetes on dialysis. It will include a review of the evidence of CGM in the dialysis population and consider how technologies can be used to inform patients and professionals.

### **2.3 Does hyperglycaemia matter in people with diabetes on dialysis?**

There is circumstantial evidence that hyperglycaemia correlates with poorer outcomes in people with diabetes on dialysis, but most of this data relies on measurement of HbA<sub>1c</sub>. Data from 2007 in over 23000 patients on maintenance haemodialysis (mHDx) suggested that HbA<sub>1c</sub> greater than 10% (86 mmol/mol) was associated with a higher death rate compared to HbA<sub>1c</sub> below 6% (42 mmol/mol).<sup>7</sup> Similarly, data from 1255 patients on mHDx showed that those with HbA<sub>1c</sub> above 8% (64 mmol/mol) had a greater than two-fold risk of death than those with HbA<sub>1c</sub> below 6% (42 mmol/mol).<sup>8</sup> Evidence from an observational study of 9201 subjects on mHDx, however, suggested a “U” shaped curve of glycaemic control in those on mHDx, with the lowest mortality seen at HbA<sub>1c</sub> 53–63 mmol/mol (7.0–7.9%).<sup>9</sup> Meta-analysis of 10 studies involving over 84000 people with diabetes on mHDx suggested that those with a mean HbA<sub>1c</sub> of 8.5% (69 mmol/mol) or greater had a 29% increased mortality compared to those with a mean HbA<sub>1c</sub> of 7.4% (58 mmol/mol).<sup>10</sup>

Whilst these studies suggest that poor glycaemic control is likely to be harmful to people with diabetes on dialysis, there is as yet no clear evidence that tightening glucose control is associated with reduced mortality or morbidity. Furthermore, the use of HbA<sub>1c</sub> to measure glycaemic control in people with diabetes on dialysis is subject to significant error (see below).

### **2.4 Why is glycaemic management challenging in people with diabetes on dialysis?**

Management of glucose in people with diabetes on dialysis is particularly challenging due to a number of factors:

1. Pharmacological options are limited in end stage kidney disease (ESKD) (see SECTION 3), and frequently insulin may be the only available agent in addition to DPP-4 inhibitors. Whilst careful management of glycaemia with insulin is feasible, people with diabetes on dialysis are at particular risk of hypoglycaemia and glycaemic variability (as discussed below).
2. Symptoms of hypoglycaemia may be less marked in people with longstanding, complex diabetes, and indeed symptoms of hypoglycaemia may be confused with symptomatic hypotension, particularly during or immediately after mHDx.

3. The ability of people with diabetes on dialysis to access specialist care is often limited by their regular and frequent attendance for dialysis (see SECTION 1).
4. The dialysis process is associated with loss of appetite and itself can exacerbate difficulties around mealtimes and medication/insulin dosing which have to be fitted around dialysis sessions.
5. Dialysis clears a number of glucoregulatory hormones, including insulin and glucagon.<sup>11</sup>
6. Glucose concentration in the dialysate may affect plasma glucose, with lower glucose dialysates being associated with hypoglycaemia.<sup>12</sup> Conversely, high glucose containing fluids used in peritoneal dialysis (PD) may cause problematic hyperglycaemia (see SECTION 6).
7. Dialysis may clear antidiabetic therapy such as insulin or sulfonylureas.
8. Dialysis causes periodic improvement in uraemia, acidosis and hyperphosphataemia which can lead to subsequent improved insulin secretion and reduced insulin resistance, leading to a higher risk of hypoglycaemia.<sup>13</sup>

A phenomenon of “burnt-out diabetes” has been described, whereby individuals with Type 2 diabetes (T2D) on dialysis experience frequent hypoglycaemic episodes leading to cessation of their antidiabetic therapies transiently or permanently.<sup>14</sup> Most people with diabetes on dialysis will, however, require some therapy for hyperglycaemia. “Burnt-out diabetes” does not occur in people with Type 1 diabetes (T1D), who will always need to continue lifelong insulin therapy, unless undergoing pancreatic/islet cell transplantation.

During a mHDx session, blood glucose tends to fall in both people with diabetes and those without diabetes, with the nadir during the third hour.<sup>15</sup> Therefore, glucose control on dialysis days may be very different to that on non-dialysis days, leading to unpredictable glucose levels, and glycaemic variability (GV).<sup>16</sup> Similarly, in relation to PD, glucose levels may vary according to fluid used and timing of PD.

A study using 24-hour CGM found that 75% of hypoglycaemic events and 82% of nadir glucose levels occurred within 24 hours of haemodialysis.<sup>15</sup> A further study suggested that GV was greatest on haemodialysis days compared to non-dialysis days.<sup>17</sup> Therefore, variation of oral hypoglycaemic or insulin therapy may be required on dialysis and non-dialysis days.

Hypoglycaemia is associated with a high morbidity in the non-dialysis population.<sup>18</sup> In people with diabetes on dialysis, hypoglycaemia is also associated with an increased risk of mortality and hospitalisation.<sup>19</sup> In addition, it is associated with a high risk of stroke, arrhythmia and sudden cardiac death.<sup>20,21</sup> High GV frequently occurs in concert with hypoglycaemia, and avoidance of hypoglycaemia may reduce GV.<sup>22</sup> High GV is associated with increased mortality in non-dialysis populations.<sup>23</sup>

## **2.5 Assessment of glucose control using glycated proteins in people with diabetes on dialysis**

Glucose monitoring in people with diabetes has traditionally involved a combination of self-monitoring of blood glucose (SMBG) and use of glycated proteins including HbA<sub>1c</sub>, serum fructosamine or in some countries, glycated albumin (GA). This section aims to discuss the difficulties in using glycated proteins for monitoring of glycaemia in people with diabetes on dialysis.

### **HbA<sub>1c</sub>**

HbA<sub>1c</sub> is a measure of the irreversible non-enzymatic glycation product of one or both NH<sub>2</sub>-terminal valines of the  $\beta$ -haemoglobin chain. As red blood cells (RBCs) remain in the circulation for 90-120 days, a measure of haemoglobin glycation can give a good estimation of prevailing glycaemic control over this period. Indeed, the A<sub>1c</sub> Derived Average Glucose Study Group (ADAG) reported that HbA<sub>1c</sub> correlates well with average daily glucose, but people with CKD were excluded from this study.<sup>24</sup>

In people on dialysis, a number of factors may lead to difficulties in interpreting HbA<sub>1c</sub> as an estimate of glucose control:

1. RBCs may be damaged during the dialysis procedure, leading to a shortened RBC life span. This can falsely lower HbA<sub>1c</sub> levels by reducing the RBC glycaemic exposure time.<sup>25</sup>
2. Treatment with erythropoietin or iron therapy leads to an increase in RBC production, and an increase in younger red blood cells, potentially falsely lowering HbA<sub>1c</sub> by reducing the RBC glycaemic exposure time.<sup>26</sup>
3. Conversely, iron deficiency is associated with higher HbA<sub>1c</sub>, as this tends to reduce turnover of RBCs.<sup>27</sup> Iron replacement appears to lower HbA<sub>1c</sub> independent of glycaemic control, by increasing proportion of younger RBCs.<sup>26</sup>

It is suggested that in people with diabetes on mHDx, a stable erythropoietin dose and stable haemoglobin value may still have a valid HbA<sub>1c</sub> reading.<sup>28</sup> Commencement, or increase in doses of erythropoietin or iron, however, may lead to reduced RBC glycaemic exposure time and a falsely lowered HbA<sub>1c</sub> value.

A number of studies comparing CGM measures with HbA<sub>1c</sub> suggest that HbA<sub>1c</sub> poorly reflects GV in people with diabetes on dialysis.<sup>29,30</sup> In a study of 1758 people on dialysis from 26 US centres, HbA<sub>1c</sub> was suggested as being poorly reflective of prevailing glucose control in a significant number of individuals.<sup>31</sup> It is therefore important for clinicians managing people with diabetes on mHDx to appreciate that HbA<sub>1c</sub> may not give a true reflection of prevailing glycaemia and is particularly poor at identifying GV and risk of hypoglycaemia, a common issue in people with diabetes on mHDx.

### **Serum fructosamine**

Serum fructosamine is a glycated protein that estimates glycaemic control over a period of around 14 days. Its value should be corrected for serum albumin and is not affected by haemoglobin values. In people on mHDx, there is little available data on whether fructosamine offers any benefit over HbA<sub>1c</sub> in glycaemic monitoring. Findings are inconsistent - fructosamine is considered a reliable marker of medium-term blood glucose (2 to 3 weeks) monitoring in some studies, but not others. One study reviewed 23 people with diabetes on mHDx and suggested that fructosamine correlated poorly with glycaemic control.<sup>32</sup> A further study of 74 people with diabetes on mHDx suggested that corrected fructosamine was a poor indicator for glycaemic control.<sup>33</sup>

### **Glycated albumin (GA)**

GA has been suggested as a better marker of glucose control in people with CKD due to its lack of variability with haemoglobin. Indeed, some countries use this widely to monitor glucose, especially in Japan. GA can, however, be affected by conditions that change serum albumin concentrations, such as nephrotic syndrome, protein losing enteropathy, malnutrition, cirrhosis, thyroid disease, hyperuricaemia and smoking. There are a number of studies examining the use of GA in people with diabetes on mHDx. A Japanese cross-sectional study aimed to examine 90 people on mHDx, to evaluate associations between GA, HbA<sub>1c</sub> and daily glucose profiles based on blood glucose measurements at seven different times a day.<sup>34</sup> Their results suggested that GA independently correlated with maximum glucose levels and mean amplitude of glucose excursion (MAGE), whilst no correlation with HbA<sub>1c</sub> was seen with these factors. The authors concluded that GA levels may be a better indicator of glycaemic control than HbA<sub>1c</sub>, especially as a means of evaluating the glucose excursions in people with diabetes on mHDx patients.

A further study of HbA<sub>1c</sub> and GA in 258 people with diabetes on mHDx, compared to 49 people with no renal disease, showed that in people with diabetes on mHDx, mean serum glucose and GA was higher compared to HbA<sub>1c</sub>, and HbA<sub>1c</sub> was positively associated with haemoglobin and negatively associated with erythropoietin dose.<sup>35</sup> There was no observed effect of these on GA, and multivariate analysis suggested that HbA<sub>1c</sub> level was dependent on dialysis status, whereas GA was not. The authors concluded that HbA<sub>1c</sub> significantly underestimated glycaemic control, and that GA more accurately reflected glycaemic control.

CGM has been used to compare GA and HbA<sub>1c</sub> in 37 people with diabetes on mHDx.<sup>36</sup> The authors found that GA was a stronger indicator of poor glycaemic control assessed with 7-day-long CGM when compared to glycated serum proteins or HbA<sub>1c</sub>. A study of 31 Japanese people on mHDx showed similar findings.<sup>37</sup>

There is also some suggestion that GA may be a better marker of mortality than HbA<sub>1c</sub>. One study examined 22,441 people with diabetes on mHDx who had both GA and HbA<sub>1c</sub> regularly monitored over a one year.<sup>38</sup> Mortality showed a linear relationship with GA, and a U-shaped curve for HbA<sub>1c</sub>, suggesting superiority of GA over HbA<sub>1c</sub> in predicting mortality in people with diabetes on HD. A further meta-analysis of 25932 mHDx patients across 12 studies with maximum follow-up of 11 years suggested that higher GA levels were associated with the risk of all-cause mortality.<sup>39</sup> Similar findings have been reported in other studies.<sup>40,41</sup>

Meta-analysis of studies investigating the correlation between GA or HbA<sub>1c</sub> and average glucose levels in people with diabetes on mHDx has been reported.<sup>42</sup> This incorporated 24 studies with 3,928 patients and found that in people with advanced CKD, the pooled regression between GA and average glucose was 0.57 (95% CI = 0.52–0.62), and 0.49 (95% CI = 0.45–0.52) for HbA<sub>1c</sub> ( $P = 0.0001$ ). They concluded that GA was superior to HbA<sub>1c</sub> in assessing blood glucose control in diabetes people with advanced CKD.

## **2.6 Assessment of glucose control using dynamic measures in people with diabetes on dialysis**

Dynamic assessments of glucose control may be needed in people with diabetes on dialysis for the following reasons:

1. Inaccuracies in HbA<sub>1c</sub>, GA and fructosamine make it difficult to optimise diabetes therapy and reduce risks for long-term complications.
2. Long-term markers of glycaemic control may not help with day-to-day management and/or changes in diabetes therapies or insulin doses.

3. Assessment of long-term glycaemic control, glucose trends, GV (inter- or intra-day), time in target glucose range, hypoglycaemia and hyperglycaemia burden (time spent or magnitude of excursions) for therapeutic adjustments are important in this high-risk group especially given dialysis related changes in insulin sensitivity, GV, frailty, co-morbidity burden and complexity.
4. Tools to support self-adjustment of treatment and detecting hypoglycaemia are important for safe and optimal self-management in this high-risk patient group.

Current options available for dynamic glucose measurement are summarised in Table 2.1

### **Self-monitoring of blood glucose (SMBG)**

Frequent SMBG relies on multiple point measurements of capillary blood glucose (CBG). To ensure reasonable accuracy of the meter in this population, it should not be affected by haematocrit interference.<sup>43</sup> Advice regarding frequency of testing and target blood glucose levels should be individualised to the person and their diabetes therapy. For those on insulin, SMBG during and after mHDx should be emphasised.

Whilst perceived as cheap, widely available, and limited requirements for health care professionals (HCPs) and patient training compared to CGM, their utility in providing accurate assessments of long-term glucose control rely on high frequency of self-monitoring (up to 6-8 times per day). This requires a considerable level of motivation, increases treatment burden, cost and affects quality of life. SMBG provides a static measure of glucose with no assessment of trend or direction of change. Modification of therapy requires meter downloads to review glucose data and make therapeutic adjustments. Whilst there are no long-term prospective studies to assess impact of multiple CBG measurements on patient outcomes, studies assessing accuracy of glycosylated proteins regularly employ this approach.<sup>34</sup>

There are other limitations of using SMBG. Multiple point SMBG can fail to detect asymptomatic and nocturnal hypoglycaemia and may not provide complete glycaemic profiles during the daytime or mHDx sessions.<sup>44</sup> In addition, several factors may impact on accuracy of SMBG meters, including anaemia, interfering substances and medications (Table 2.2).<sup>45-48</sup> It is recommended that glucose meters using glucose oxidase (GO) or glucose dehydrogenase pyrroloquinoline quinone (GDH-PQQ) enzymatic methods for glucose assessment should not be used in people with diabetes on dialysis.

### **Continuous glucose monitoring (CGM)**

CGM devices or glucose sensors are inserted subcutaneously on the upper arm or abdomen for 7-14 days and measure interstitial fluid glucose concentrations, usually via an electrode. There is a 2-3-minute delay in interstitial fluid glucose response to changes in blood glucose.

Flash glucose monitoring (Flash GM) and real-time CGM provide dynamic information on glucose (Table 2.1). This includes interstitial glucose concentrations, trend arrows showing the direction and rate of travel of glucose and visualisation of retrospective glucose graphs which can be used to make real-time adjustments to insulin dosing by the user. Patient education for optimal self-management to use this information is required. Newer Flash GM and real-time CGM also offer customisable predictive alerts to low or high glucose, providing an additional safety benefit and send glucose data directly to the receiver without the requirement for the user to scan the sensor.

All forms of CGM provide summary data of time in target glucose range, time above or below range and measures of GV, which can be used to assess overall glycaemic control, trends, variability, hypoglycaemia risk and long-term therapeutic guidance. These may require the CGM device to be manually downloaded by the person with diabetes or HCP. CGM options that integrate with smartphones can upload data automatically into a cloud-based system that can be shared with the HCP as well as other carers or friends and family with potential to send alerts to others. They also provide easier retrospective review of data and potential of learning from this.

Time in range (TIR) has been negatively correlated with progression of microvascular complications, HbA<sub>1c</sub> and number of hypoglycaemic episodes.<sup>49</sup> International consensus guidelines on CGM targets recommend >50% TIR (3.9-10 mmol/L) with <1% time in hypoglycaemia (<3.9 mmol/L) and <10% of time in significant hyperglycaemia (>13.9 mmol/L) in high risk populations with diabetes.<sup>49</sup> In people at high risk of hypoglycaemia and its consequences, such as people with diabetes on insulin and/or sulfonylurea on dialysis, a higher target may be considered (glucose range 6-12 mmol/L). GV, measured by the CV (Standard Deviation/Mean \* 100) target should be <36%.

### **Masked (or blinded) CGM**

These devices are worn intermittently, but the receiver will not display any glucose concentration or trend arrow (Table 2.1). Data downloaded at the end of the sensor period can be reviewed retrospectively for diagnostic purposes and to support diabetes therapy adjustments and self-management.



They are cheaper than options discussed later as can be used periodically and have reduced patient educational requirements. They can provide assessments of glucose control, trends, variability, TIR and hypoglycaemia burden. They do not provide the user with any real-time data to make treatment decisions, and hence, there will be an ongoing requirement for SMBG for day to day treatment decisions.

An observational study indicated higher frequency of hypoglycaemia on dialysis days and potential for masked CGM or more detailed glucose assessments to refine therapy in people with diabetes on mHDx.<sup>15</sup> A further short masked CGM study demonstrated more frequent diabetes treatment changes and optimisations with masked CGM compared with SMBG alone and improvements in glycaemic control and hypoglycaemia in people with diabetes on mHDx when combined with frequent review and therapy adjustment.<sup>50</sup>

### **Flash glucose monitoring**

Flash GM (Freestyle Libre<sup>®</sup> and Freestyle Libre 2<sup>®</sup> Abbot) is approved by a number of national guidelines for people with any form of diabetes on dialysis treated with insulin. It is worn for 14 days on the upper arm, the user must scan the sensor intermittently and the receiver (which can be a mobile phone app or separate reader) will display current interstitial glucose concentration, trend arrows and retrospective glucose graph. The sensor must be scanned at minimum every eight hours to ensure continuous glucose data is recorded. It is expected that users wear the device continuously and scan 8-10 times per day for optimal benefits. Freestyle Libre 2<sup>®</sup> provides alerts to prompt users to scan if glucose levels are high or low. Initial training is needed for patient self-management to use the device, interpret the data and make therapy changes accordingly.

Observational evidence from people with T1D demonstrates improvements in glycaemic control that are dependent on using the device continuously and scanning frequently.<sup>51</sup> There is no current evidence that use of Flash GM improves glucose control or reduces hypoglycaemia in people with diabetes on dialysis. These systems, however, are very easy to use and although they have a requirement for periodic scanning, they do not have requirements for calibrations and have lower running costs compared to other sensor options. Flash GM may be used periodically to provide glucose assessments discussed in the masked CGM section. However, as they are not masked, they will be prone to differences in patient behaviour that may alter the glucose data.

### **Real-time CGM (RT-CGM)**

These CGM systems are worn for 7-10 days on the upper arm or abdomen and the receiver (which can be a mobile phone app or separate device) will display real-time interstitial glucose concentration, trend arrows showing the direction and rate of travel of glucose and

retrospective glucose graph (Table 2.1). Alarms can be programmed to alert the user in the event of impending or actual hypo- or hyperglycaemia and these systems are therefore of particular use in people with diabetes who do not get symptoms of hypoglycaemia or who have had previous episodes of severe hypoglycaemia requiring third party assistance. It is expected that users wear the device continuously. These systems also have the additional benefit of linking with automated insulin dosing systems and in future may also link with smartphone-based bolus insulin advisors that can link with smart pens. Like Flash GM, there is a requirement for initial patient training to use the device, interpret the data, respond to alarms and alerts and make therapy changes accordingly.

Studies in people with T1D have shown that the use of CGM is associated with reduction in HbA<sub>1c</sub>, reduced duration of hypoglycaemia and increased TIR, whilst reducing fear of hypoglycaemia, diabetes-related distress and improving quality of life compared with SMBG.<sup>52</sup> These benefits are dependent on adherence.

There is no current evidence that use of real-time CGM improves glucose control or reduces hypoglycaemia in people on dialysis. There are higher costs compared with other approaches. At present there are no data demonstrating their benefit in people with diabetes on dialysis.

### **Accuracy**

There are limited data available on the accuracy of CGM systems in people on dialysis. Device manufacturers provide accuracy metrics, but independent accuracy studies in the setting of dialysis are needed. A recent study reported variations in accuracy of commonly used CGM options, suggesting good correlation between a CGM system and laboratory glucose but additional studies of other CGM systems are ongoing.<sup>36</sup> At present no CGM system has been licenced for use in people with diabetes on dialysis. Similarly, accuracy of SMBG varies depending on glucose meter options and this has not been studied in dialysis settings.<sup>53</sup> Interference and potential effects of substances on CGM derived readings have been detailed elsewhere.<sup>45</sup> Therefore, whilst useful in providing continuous measure of glucose assessment, clinicians must interpret the performance of the CGM system used in individual people with diabetes on dialysis carefully.

### **2.7 Experience of CGM in people with diabetes on dialysis**

The potential for CGM technologies to improve diabetes care in the dialysis population has been recognised although only few observational studies have been conducted. In these studies, CGM-derived glucose correlated well with SMBG and laboratory glucose

measurements in mHDx patients.<sup>16,36</sup> However, CGM-derived glucose correlated poorly with HbA<sub>1c</sub>, and did not correlate at all with fructosamine in mHDx patients.<sup>16</sup> A study comparing Flash GM to simultaneous masked CGM and SMBG showed that although masked CGM appeared to be more accurate than Flash GM, Flash GM was clinically acceptable for use in mHDx.<sup>54</sup> CGM derived glucose measures have also been used as the reference standard to compare alternative markers to serum HbA<sub>1c</sub>, despite the lack of their clinical applicability.<sup>36</sup>

A systematic review of studies of CGM in people with diabetes on mHDx was published in December 2020.<sup>55</sup> The authors included 12 studies comprising 304 patients. Four studies found significant fluctuations in glucose levels during mHDx, with a higher GV on the day of dialysis. Three studies suggested that CGM was better at monitoring glucose than HbA<sub>1c</sub>. The authors concluded that “considering manageability, accuracy, and cost effectiveness, CGM could be the ideal diagnostic tool for people with diabetes on mHDx”.

CGM studies demonstrate that people with diabetes on mHDx experience high levels of GV and hypoglycaemia.<sup>15,56-58</sup> CGM can be utilised to study the impact different diabetes treatments have on GV.<sup>59-62</sup> Two as yet unpublished studies have also informed this guidance (personal communications). The **Linagliptin in Type 2 Diabetes and Chronic Kidney Disease (LINDA-CKD)** study was an observational cross-sectional study using CGM to assess hypoglycaemia incidence and GV in 100 people with T2D; 50 with CKD stage 3 to 5, and 50 on HD. Although baseline serum HbA<sub>1c</sub> in CKD and mHDx participants were similar (58 vs. 59 mmol/mol respectively), estimated CGM HbA<sub>1c</sub> was significantly different between the two groups, with mHDx patients having a higher estimated CGM HbA<sub>1c</sub> compared to CKD patients (69 vs. 56 mmol/mol,  $p < 0.001$ ). Estimated CGM HbA<sub>1c</sub> better reflected that mHDx participants spent significantly more time above range compared to CKD participants ( $>10.0$  mmol/L; 51.8% vs. 32.3%,  $p < 0.001$ ;  $>13.9$  mmol/L 22.0% vs. 9.4%,  $p = 0.001$ ). This suggests that serum HbA<sub>1c</sub> appears to underestimate true glycaemic control, leaving people with diabetes on mHDx exposed to more hyperglycaemia.

The **DRIVE-HD (Diabetes and Real-world Investigations of Glucose Instability Variability and Exposure in Haemodialysis)** was an observational study aimed to review dysglycaemia in people with diabetes treated with insulin on HD. 69 participants completed a minimum of 7 days blinded CGM. During mHDx against a fixed glucose concentration, GV was found to be reduced compared to the same period on non-dialysis days. Importantly, however, only 30% people with diabetes on mHDx in this study were not at risk of hypo- or hyperglycaemia, or both.

## **2.8 Use of CGM in people with diabetes on PD**

PD fluids often contain large amounts of glucose as the dialysate (see SECTION 6). This glucose is frequently absorbed and can lead to significant fluctuations in plasma glucose over the period of PD. A number of small studies have used CGM to assess glycaemic control in patients on PD. It is important to note, however, that there is more potential for interference with CGM performance in PD and limited data validating the accuracy of CGM in this setting. The first study to consider CGM in PD was published in 2003.<sup>63</sup> The authors used CGM in eight patients on PD and found that CGM was a useful tool to gain insights into glycaemic control of people with diabetes on PD and suggested that non-glucose-containing dialysates were associated with improvements in glycaemic control.

A Japanese study of 10 patients on PD monitored with CGM over 3 days, showed a large diurnal variation in glucose, especially at night.<sup>64</sup> In five patients, CGM was performed again after adjustment to antidiabetic drugs, and showed an improvement in glucose variability in people treated with a dipeptidyl peptidase IV inhibitor or a change in insulin dose. A further Japanese study of 20 patients on PD with CGM showed that automated PD showed less glycaemic fluctuation compared to those on continuous ambulatory PD.<sup>65</sup>

A study from Nanjing in China examined glucose profiles of people with diabetes on mHDx (n=35) and PD (n=29) using CGMS and found much overall higher glucose levels amongst patients on PD, but greater GV in patients on mHDx, including higher risk of hypoglycaemia.<sup>66</sup> The authors noted that HbA<sub>1c</sub> did not adequately indicate those patients who were highest risk for GV or hypoglycaemia.

As yet there is no randomised trial evidence that use of CGM can improve glucose control in PD and is an area requiring further research.

## **2.9 What does good glucose control look like in people with diabetes on dialysis?**

The evidence presented highlights the risks of adverse outcomes for individuals on dialysis associated with hyperglycaemia, hypoglycaemia and GV, and there are difficulties in using standard glucose measures such as HbA<sub>1c</sub> to define glycaemic risks. Direct but representative glucose measures are needed, although this can represent challenge in day to day practice. To minimise these challenges, we need first develop a consensus on optimal glucose control in this population group, and then define monitoring structures which allow its assessment. Figure 1 outlines a stepwise approach to glucose monitoring in people with diabetes on dialysis.

## Hierarchy of glycaemic goals in people with diabetes on dialysis

In keeping with international consensus guidelines, the principle of TIR is the most useful definition of targets for this group. The target range, however, needs to take into account the impact of renal disease and hypoglycaemia risk. Therefore, we propose a hierarchy of goals as follows:

1. Avoidance of ALL severe hypoglycaemia (requiring 3<sup>rd</sup> party assistance)
2. Avoidance of significant hypoglycaemia (significant =  $<3\text{mmol/L}$ )
3. Minimisation of time spent with glucose  $> 13.9\text{mmol/L}$  ( $<25\%$  or 6h per day)
4. Minimisation of time spent with glucose  $< 5\text{mmol/L}$  ( $<4\%$  or 1h per day)
5. Minimisation of excessive glycaemic variability ( $\text{CV}>36\%$  or  $\text{SD}>3.5\text{mmol/L}$ )

It is therefore proposed that a target range for people with diabetes on dialysis of 6–12 mmol/L and a goal of achieving  $\geq 70\%$  TIR.

## Risk assessment & monitoring strategy

With the challenges described above in relation to interpretation of HbA<sub>1c</sub> in people with diabetes on dialysis, regular assessment of glucose control in such patients should be based on direct glucose measurements.

It may be unrealistic to expect CGM to be undertaken in all people with diabetes on mHDx, and therefore focus should be made on those at high risk of hypoglycaemia or glycaemic variability. Prioritisation may be based on the following:

1. All people with diabetes on dialysis using insulin who have recurrent hypoglycaemia or loss of hypoglycaemia awareness should be offered real-time CGM.
2. Long term CGM should be considered in people with diabetes on dialysis who are treated with insulin and/or sulfonylurea, unless practical issues make long-term use difficult, in which case 6 to 12 monthly CGM can be used to aid dose adjustments and assess adequacy of treatment.

SMBG for risk-assessment may be useful in those individuals who are able to undertake frequent and regular SMBG. This requires a specific structure to be used which should address the known glycaemic risks for this group, but which in addition does not place excessive burdens on the person involved. An example of such a structure (based on two tests per day) is detailed below in Table 2.3 and can be advised for one- or two-week period.

We propose that, based on SMBG results, the following groups of patients should be considered for regular diagnostic (6-12 monthly) CGM:

1. Those in whom SMBG results show frequent (>5%) glucose readings below 4 mmol/L
2. Those in whom SMBG results show frequent (>20%) glucose readings above 14 mmol/L
3. Those who are unable to undertake SMBG twice daily for 1-2 weeks periods.
4. Those who have HbA1c < 42 mmol/mol (6.0%) or > 80 mmol/mol (9.5%).

**Table 2.1 Current options available for dynamic glucose measurement in PwD**

	<b>SMBG</b>	<b>Masked CGM</b>	<b>Periodic Flash CGM</b>	<b>Flash GM</b>	<b>RT-CGM</b>
<b>Advantages</b>	<p>Inexpensive</p> <p>Easily available</p> <p>Less HCP training</p>	<p>Less expensive than ongoing CGM</p> <p>Less patient training needs</p> <p>Provides detailed measure of glucose assessments</p> <p>Newer versions do not need calibrations</p> <p>Smartphone and remote data share options for some types</p>	<p>Less expensive than ongoing CGM</p> <p>Less patient training needs</p> <p>Provides detailed measure of glucose assessments</p> <p>Smartphone and remote data share options</p>	<p>Less expensive than RT-CGM</p> <p>Provides detailed measure of glucose assessments</p> <p>Continuous assessment</p> <p>Data for self-management and learning</p> <p>No separate transmitter insertion</p> <p>Smartphone and remote data share options</p> <p>Calibration free Recent option for alerts</p>	<p>Provides detailed measure of glucose assessments</p> <p>Data for self-management and learning</p> <p>Continuous assessment</p> <p>Smartphone and remote data share options</p> <p>Calibration free (some versions)</p> <p>Integration with automated insulin dosing systems and bolus advisors</p> <p>Customisable alarm/ alerts and predictive alarm/alerts</p>

				prompting user to scan <sup>4</sup>	Improved accuracy in low glucose settings compared to flash CGM
<b>Disadvantages</b>	<p>Therapeutic and diagnostic success depend on frequent SMBG</p> <p>High user motivation needed</p> <p>Impacts QoL</p> <p>Provides static measure only</p> <p>Manual download for data review needed</p> <p>No alarms or alerts</p>	<p>Periodic assessment rather than continuous</p> <p>Diagnostic data only (no real-time data for self-management)</p> <p>No alarms/alerts</p> <p>HCP training needed</p>	<p>Periodic assessment rather than continuous</p> <p>Unmasked therefore potential for behaviour alterations and risk of anxiety or therapeutic changes</p> <p>Requires periodic scanning (every 8 hours)</p> <p>No alarms/alerts</p> <p>Diagnostic data only (data for self-management and learning 4 weeks/year only)</p> <p>HCP training needed</p>	<p>No predictive alarm/ alerts</p> <p>Patient training needed (device use, data interpretation and adjusting treatment)</p> <p>HCP training needed</p> <p>Accuracy may not be reliable in low glucose settings</p>	<p>Expense</p> <p>Patient training needed (device use, data interpretation and adjusting treatment)</p> <p>HCP training needed</p>

1. Costs may vary in different areas depending on price options available.

2. Estimated HbA<sub>1c</sub> / mean glucose for long-term glycaemic control, glucose trends, glycaemic variability, time in range, time below range and time above range for hypoglycaemia and hyperglycaemia burden as well as magnitude of excursions.

3. Smartphone options bypass need for manual download, otherwise need for separate receiver and manual download.

4. Freestyle Libre 2® is a flash CGM system with alerts to prompt to scan if glucose levels are low or high. Alerts can be customised between low (3.3-5.6 mmol/L) or high (6.7 to 22.2 mmol/L) options.



**Table 2.2 Common interfering factors impacting on SMBG accuracy**

<b>SMBG enzymatic method for glucose assessment</b>	<b>Known interference</b>
Glucose oxidase (GO)	Low haematocrit (<35%) (meters may correct for this) Hypoxia High paracetamol levels High levels of bilirubin, uric acid, triglycerides
Hexokinase (HK)	No known interference with non-glucose sugars
<b>Glucose dehydrogenase (GDH) based:</b>	
GDH and co-enzyme pyrroloquinoline-quinone (GDH-PQQ)	Other sugars such as Icodextrin in peritoneal dialysis
GDH and co-enzyme nicotine adenine dinucleotide (GDH-NAD)	No known interference with non-glucose sugars
GDH and co-enzyme flavin adenine dinucleotide (GDH-FAD)	No known interference with non-glucose sugars

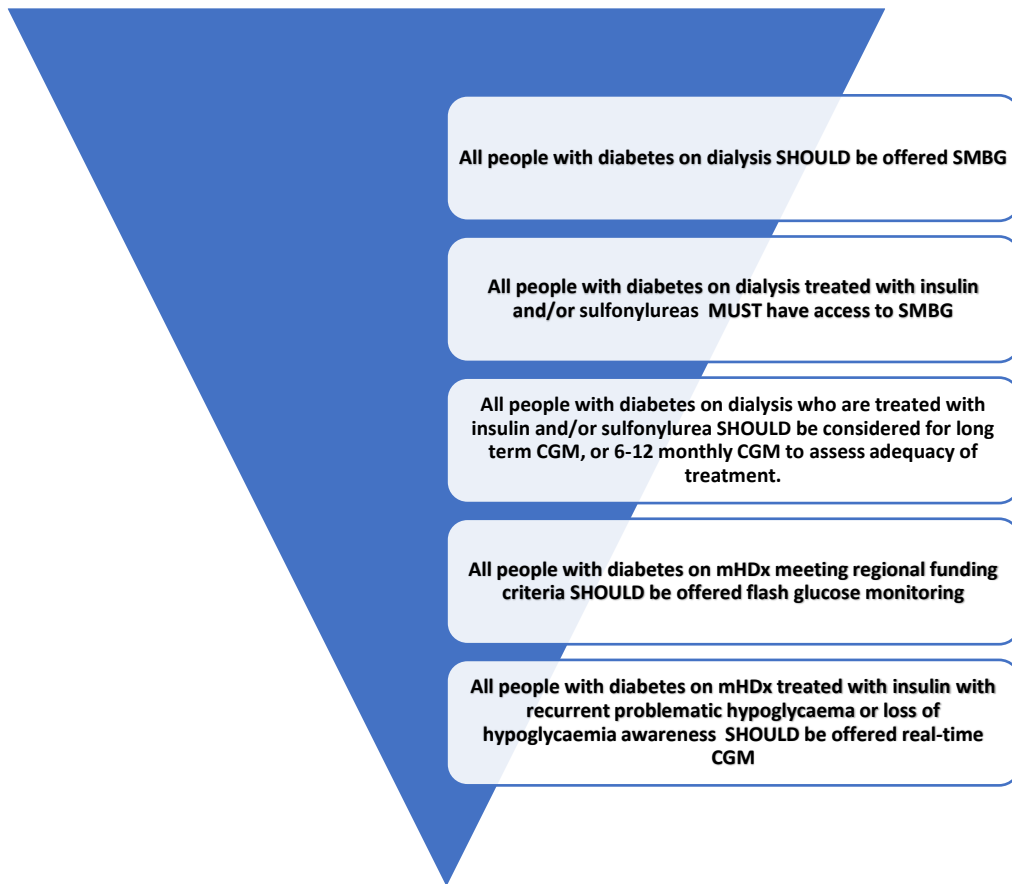
**Table 2.3 Example SMBG structure based on two tests per day for people with diabetes on dialysis unable to undertake diagnostic CGM.**

Week One

- |       |   |
|-------|---|
| Day 1 | i) Fasting (morning) ii) Before main evening meal |
| Day 2 | i) Before dialysis ii) 30 mins after dialysis     |
| Day 3 | i) Before lunch ii) Before bed                    |
| Day 4 | i) Immediately after dialysis ii) 3 hours later   |
| Day 5 | i) Fasting (morning) ii) Before bed               |
| Day 6 | i) Before dialysis ii) 4 hours after dialysis     |
| Day 7 | i) Before lunch ii) Before evening meal           |

Week Two

Repeat above for days 8-14



**Figure 2.1 A stepwise approach towards offering different glucose monitoring strategies to people with diabetes on dialysis.**

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## **SECTION 3A NON-INSULIN GLUCOSE LOWERING THERAPIES**

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## **RECOMMENDATIONS FOR SECTION 3A**

**3A.1 Sulfonylureas, Glinides, Acarbose, Metformin and Sodium Glucose Transporter-2 inhibitors (SGLT-2Is) are not licensed for use in patients on dialysis. We therefore do not recommend their use in people with diabetes on dialysis. (Grade 1B)**

**3A.2 Pioglitazone is not licensed for use in patients on dialysis although it is licenced for use in patients with eGFR down to 4 mL/min and has been used safely in patients on maintenance haemodialysis [mHDx]. We therefore suggest its use with caution in people with diabetes on mHDx. (Grade 1C)**

**3A.3 The DPP-4 inhibitors linagliptin, sitagliptin, vildagliptin and alogliptin are all licenced for use in patients on dialysis. We therefore recommend their use in people with diabetes on dialysis. Dose reductions for sitagliptin, vildagliptin and alogliptin are required. (Grade 1B)**

**3A.4 GLP1-receptor agonists are not licenced for use in patients with eGFR of <15 mL/min but have been used safely in patients on mHDx. We therefore suggest their use with caution in people with diabetes on mHDx (Grade 2D)**

### **3A.1 Principles of glycaemic management in people with diabetes on dialysis**

In people with declining renal function, whilst peripheral insulin resistance may increase, clearance of insulin (endogenous and exogenous) and other anti-hyperglycaemic agents declines, leading to an increased risk of hypoglycaemia.

A so-called “burnt-out diabetes” phenomenon has been described, whereby people with Type 2 diabetes (T2D) on dialysis may need reduced doses of medications used to treat their diabetes, with cessation of their anti-diabetic therapies transiently or permanently in a significant number of cases.<sup>1</sup>

While insulin therapy is the only therapeutic option in Type 1 Diabetes (T1D), pharmacologic and non-pharmacological treatment options are relevant to the management of T2D. This summary will focus on the pharmacological agents used in the treatment T2D in people on dialysis.

Not all classes of anti-hyperglycaemic agent are suitable for use in people with diabetes on dialysis; some have restricted licences or insufficient evidence of use in this setting. Each of the drug groups will be discussed below briefly covering mode of action, licensed indication, clinical use, key contraindications and need for monitoring.

Updated licensing was reviewed for this document on 10<sup>th</sup> September 2021.

### **3A.2 Insulin secretagogues, metformin, alpha-glucosidase inhibitors, thiazolidinediones, SGLT2 inhibitors**

**Sulfonylureas** (SU) are metabolised by hepatic cytochrome P450 CYP2C9, though clearance of metabolites and unchanged drug is usually partly through the kidney.

Therefore, accumulation in renal failure patients including those on dialysis may predispose those individuals to risk of hypoglycaemia. It should be noted that SUs are generally highly protein bound and therefore unlikely to be dialysed, which can cause post-dialysis hypoglycaemia. These drugs do not have licensing that supports their use in the presence of severe renal impairment (creatinine clearance of <30 mL/min) and dosage adjustments may become necessary in moderate renal impairment (creatinine clearance 30–50 mL/min). In addition to hypoglycaemia, weight gain is considered a key side effect of SU,<sup>2</sup> and there have also been concerns about possible adverse cardiovascular effects.<sup>3</sup>

- **Gliclazide** is metabolised by the liver to inactive metabolites, which are eliminated mainly in the urine (80%). This agent poses a lower risk for severe hypoglycaemia than glimepiride, although it should be used with caution when GFR is <40 mL/min.<sup>4</sup>
- **Glimepiride** is metabolised by the liver to two main metabolites, one of which has hypoglycaemic activity, and which can accumulate in people with renal impairment. The use of glimepiride is contraindicated in patients with GFR <60 mL/min.<sup>5</sup>
- **Glipizide** is metabolised by the liver. The primary metabolites are inactive hydroxylation products and polar conjugates and are excreted mainly in the urine. Less than 10% unchanged glipizide is found in urine. In terms of licensing it is contra-indicated in severe renal failure (GFR <30 mL/min).<sup>6</sup>

The use of SU in patients with T2D with end stage kidney disease (ESKD) is off-licence and therefore not recommended. It is recognised, however, that many people with diabetes on dialysis are prescribed SUs owing to the lack of alternative therapies. Clinicians and patients need to be aware of the risks of hypoglycaemia and wherever possible alternatives need to be considered, and glycaemic monitoring needs to be robust (see SECTION 2).

**Prandial glucose regulators (PGRs also called glinides)** exhibit insulinotropic effects by stimulating pancreatic SU receptors. Receptor activation is more rapid and shorter than for SU.<sup>7</sup> The main PGR available for clinical use is repaglinide.

- After a five day treatment of repaglinide (2 mg tds) in subjects with severely impaired renal function (creatinine clearance: 20–39 mL/min), there was a two-fold increase in exposure and half-life compared with subjects with normal renal function. Dose adjustments should therefore be considered at CKD stages 4–5.<sup>8</sup>

Repaglinide is not licensed for use in people with diabetes on dialysis and is highly protein bound and therefore unlikely to be removed during dialysis. The risk of hypoglycaemia is therefore increased and their use should be avoided in people with diabetes on dialysis.

**Metformin** has no clinical value in the dialysis population due to risk of severe lactic acidosis as accumulation occurs in renal failure. The NICE guideline NG28 highlights its prescribing limitations in the context of renal function and provides details of when doses should be reduced (eGFR <45 mL/min) or stopped (eGFR <30 mL/min).<sup>9, 10</sup> Metformin is not licensed to be used in people with diabetes on dialysis and therefore its use is not recommended.

**Acarbose** is an alpha-glucosidase inhibitor which competitively and reversibly inhibits enteric glucosidases located in the brush border of the small intestine. This mechanism reduces pre- and post-prandial blood glucose peaks. The agent acts locally but may cause gastrointestinal side-effect.<sup>11</sup> Acarbose can be given in CKD stage 1–3 without dose adjustment. As acarbose has not been studied in patients with severe renal impairment and should not be used in patients with a creatinine clearance of less than 25 mL/min/1.73m<sup>2</sup>. Therefore, it is not recommended for use in dialysis.

**Sodium-glucose co-transporter-2 (SGLT-2) inhibitors** block glucose reabsorption in the proximal renal tubule providing an insulin independent mechanism to lower blood glucose. Their use in clinical practice is associated with improved glycaemic control, weight loss, a low risk of hypoglycaemia and a mild reduction in blood pressure. Four SGLT-2 inhibitors

are currently available for prescription: dapagliflozin, canagliflozin, empagliflozin and ertugliflozin.

The glucose-lowering efficacy and safety of SGLT-2 inhibitors are almost comparable in patients with mild CKD (eGFR >50 mL/min) and patients with normal kidney function. However, their glycaemic benefit diminishes as GFR declines with virtually no glycaemic benefit at eGFR <30 mL/min.<sup>12</sup> These agents provide renal and cardiovascular protection, but currently the evidence does not currently extend to people on dialysis. Therefore these drugs are not recommended to be used for glycaemic control in people with diabetes on dialysis.

**Pioglitazone** is a thiazolidinedione (TZD) and can be used as monotherapy if metformin is contraindicated.

- The risk of hypoglycaemia is low with pioglitazone and its hepatic metabolism abolishes the need for dose adjustment when renal function declines.<sup>13</sup>
- It has no renal elimination and is unaffected by dialysis and can be used in CKD stage 1–5 down to a clearance of 4 mL/min.

Pioglitazone has been shown in a small RCT to be safe and effective for the treatment of diabetes in people on mHDx with additional positive effect on BP.<sup>14</sup>

In addition to better glycaemic control, pioglitazone was also shown in a prospective controlled study to improve lipid profile, decrease inflammatory markers and adiponectin level and improves responsiveness to Erythropoietin (Epo) therapy with reduction of Epo dose in mHDx patients.<sup>15</sup>

Furthermore, treatment with pioglitazone was shown in a recent large cohort study to be associated with significantly lower all-cause mortality and major adverse cardiovascular and cerebrovascular events than dipeptidylpeptidase-4 (DPP-4) inhibitors in people with diabetes on mHDx especially among those with dyslipidaemia and non-insulin users.<sup>16</sup> This study supports the findings of a previous study that compared subjects on mHDx exposed to TZD compared to no exposure and showed that thiazolidinedione was associated with significantly lower all-cause mortality among insulin-free but not insulin-requiring subjects.<sup>17</sup>

Given the emerging evidence on their safety and effectiveness on controlling glycaemia and reducing cardiovascular risk factors, we suggest the cautious use of pioglitazone in people with diabetes on dialysis by specialists in diabetes. Caution is particularly required in patients with macular oedema and renal bone disease where there have been some concerns about

the association between pioglitazone use and increased risk of bone fractures and macular oedema.<sup>18</sup>

### 3A.3 Incretin-based therapies

Incretin-based therapies enhance glucose-dependent postprandial insulin secretion and lower pre- and postprandial glycaemia.

- **DPP-4 inhibitors** (sitagliptin, linagliptin, vildagliptin, saxagliptin and alogliptin) inhibit the degradation of endogenous GLP-1 and enhance its effects on insulin secretion and glycaemia.
- **GLP-1 agonists** (exenatide, liraglutide, lixisenatide, semaglutide and dulaglutide) have limited structural similarities to GLP-1, with increased resistance to DPP4 and prolonged serum half-life relative to native GLP-1.

#### DPP-4 inhibitors

DPP-4 inhibitors are not associated with hypoglycaemia and are one of the few therapies with license for use in dialysis.

**Sitagliptin** undergoes minimal metabolism, mainly by the cytochrome P450 isoenzyme CYP3A4, and to a lesser extent by CYP2C8. About 79% of a dose is excreted unchanged in the urine. Renal excretion of sitagliptin involves active tubular secretion; it is a substrate for organic anion transporter-3 and P-glycoprotein. Sitagliptin is not removed by conventional haemodialysis but is removed by high flux dialysis (13.5 % of the drug is removed by a 3–4 hour dialysis session).<sup>19</sup> Dose adjustment is required when sitagliptin is used in people with diabetes on dialysis with recommended dose of 25mg daily. Treatment may be administered without regard to the timing of dialysis. In a randomised controlled trial of 129 subjects undergoing mHDx treatment sitagliptin compared to glipizide as monotherapy was found effective and well tolerated over 54 weeks of follow up.<sup>20</sup>

**Linagliptin** has minimal metabolism to inactive metabolites and approximately 80% is eliminated in the faeces and 5% in the urine.<sup>21</sup> It is not removed by dialysis. In moderate renal failure, a moderate increase in exposure of about 1.7 fold was observed compared with control. Exposure in T2D with severe renal failure was increased by about 1.4-fold compared with patients with T2D and normal renal function. No dose adjustment is required and



linagliptin 5mg is suitable to use in people with diabetes on dialysis. In a RCT of 133 subjects with severe renal impairment including subjects with GFR<15 mL/min, linagliptin was shown to be safe and effective with very low risk of severe hypoglycaemia and with stable body weight.<sup>22</sup>

In a prospective study of 35 subjects undergoing mHDx, linagliptin was found to decrease serum level of oxidised LDL thus may add cardiovascular protection independent of its glucose-lowering effect.<sup>23</sup>

Additionally, linagliptin was shown to have anti-inflammatory effect in patients treated by mHDX and may serve as a useful glucose control strategy for people with diabetes on dialysis.<sup>24</sup>

**Vildagliptin** about 69% of a dose of vildagliptin is metabolised, mainly by hydrolysis in the kidney to inactive metabolites. About 85% of a dose is excreted in the urine (23% as unchanged drug), and 15% in the faeces. Vildagliptin's area under the curve increases by 1.4-fold, 1.7-fold and 2-fold in patients with mild, moderate and severe renal impairment, compared with healthy subjects. The AUC of the metabolites LAY151 (the main metabolite) and BQS867 increased on average by about 1.5-fold, 3-fold and 7-fold in patients with mild, moderate and severe renal impairment, respectively. LAY151 concentrations were approximately 2–3-fold higher than in patients with severe renal impairment.<sup>25</sup> Vildagliptin is not also removed by conventional haemodialysis but is by high flux (3% of vildagliptin is removed after a 3–4 hour haemodialysis session). Dose adjustment is required in patients with ESKD and the recommended dose is 50 mg od.<sup>26</sup> In a prospective, controlled study of 51 patients with T2D undergoing mHDx with 24-week follow up, vildagliptin significantly decreased HbA<sub>1c</sub>, glycated albumin level and average postprandial plasma glucose levels with no serious adverse effects such as hypoglycaemia or liver impairment.<sup>27</sup> This finding was consistent with a 24 week study of 515 patients with T2D and moderate or severe renal impairment, which showed vildagliptin added to ongoing antidiabetic therapy had a safety profile similar to placebo and elicited a statistically and clinically significant decrease in HbA<sub>1c</sub>.<sup>28</sup> Vildagliptin was also effective when it was used to switch patients undergoing mHDX treatment from insulin to an oral therapy,<sup>29</sup> as well as when it is used in people on peritoneal dialysis.<sup>30</sup> The degree of improvement in the HbA<sub>1c</sub> and glycated albumin levels in those who were on either haemodialysis or peritoneal dialysis was dependent on these levels at baseline.

**Saxagliptin** is used at a dose of 2.5mg or 5mg od. Saxagliptin 2.5 mg was compared with placebo in a 52-week trial in 170 subjects with T2D and moderate-to-severe CKD or ESKD; the incidence of adverse events was similar between the two groups.<sup>31</sup> Saxagliptin is eliminated by both renal and hepatic pathways. It is removed by haemodialysis, and dose adjustment is needed if it is used in ESKD.<sup>32</sup> Saxagliptin was shown to be effective and well tolerated when used as monotherapy or combined with other antidiabetic drugs in a small randomised prospective trial that included 82 subjects with T2D treated by haemodialysis with no adverse events.<sup>33</sup>

**Alogliptin** is available as 6.25mg, 12.5mg and 25mg tablets. The efficacy and safety of the recommended doses of alogliptin were investigated separately in a subgroup of subjects with T2D and severe CKD/ESKD in a placebo-controlled study (59 patients on alogliptin and 56 patients on placebo for six months) and found to be consistent with the profile obtained in patients with normal renal function.<sup>34</sup> Dose adjustment is needed when used in people with diabetes on dialysis and alogliptin 6.25mg od is the recommended dose which can be administered without regard to the timing of dialysis. Alogliptin was effective and generally well-tolerated in a 48-week prospective study in 30 subjects with T2D undergoing mHDx with no serious adverse events.<sup>35</sup>

Given the emerging evidence on their safety and effectiveness on controlling glycaemia in people with diabetes on dialysis, and the fact that they are all licensed to be used when GFR is <15mL/min, we recommend the use of DPP-4 inhibitors in people with diabetes on dialysis. Given safety concerns with the use of saxagliptin in people with heart failure, we suggest saxagliptin should be avoided in individuals who have history of heart failure.<sup>18</sup>

**Table 3A.1 Dosing of DPP4 inhibitors in ESKD**

Drug	Normal dosing	ESKD dosing
Linagliptin	5mg OD	5mg OD
Vildagliptin	50mg BD	50mg OD
Alogliptin	25mg OD	6.25mg OD
Sitagliptin	100mg OD	25mg OD
Saxagliptin	5mg OD	2.5mg OD

**GLP-1 receptor agonists**

Exenatide, Liraglutide, Lixisenatide, Semaglutide and Dulaglutide are licenced for use in people with renal impairment (down to eGFR 15 mL/min) with no need for dose adjustment. Table 3A.2 describes the frequency and method of application of different GLP-1 receptor agonists.

**Table 3A.2 Frequency and method of application of different GLP1 receptor agonists**

Exenatide	Twice daily SC injection or weekly injection
Liraglutide	Daily SC injection
Lixisenatide	Daily SC injection
Dulaglutide	Weekly SC injection
Semaglutide	Weekly SC injection OR daily tablet

Although clinical experience on the use of such agents is limited in people with moderate to severe renal impairment including those on dialysis, there are several reports from small studies to show that they are safe and effective to use in people with diabetes on dialysis. Osonoi et al. reported on the effect of haemodialysis on the plasma glucose profile and liraglutide level in 10 subjects with diabetes and ESKD injected with Liraglutide at a dose of 0.6 and 0.9 mg/day and the results suggested that haemodialysis did not affect the pharmacokinetic profile of liraglutide or most glycaemic indices, thus can be used in people with diabetes on dialysis without dose adjustment.<sup>36</sup>

Kondo et al. reported on the efficacy and safety in five subjects with diabetes treated with mHDx who were switched from insulin to liraglutide at starting dose of 0.3mg /day which was gradually increased to 0.9 mg/day if needed and found that 3 months treatment with liraglutide reduced HbA<sub>1c</sub> level, BMI, and inter-dialytic weight gain in addition to significant

reduction in cardiothoracic ratio on chest radiography, thus recommending the use of liraglutide in non-compliant people with diabetes on dialysis with difficult fluid volume control.<sup>37</sup> Furthermore, in a randomised double blind placebo controlled study from Denmark, 24 subjects with T2D and ESKD and 23 control subjects with T2D and normal kidney function were randomly allocated to 12 weeks of double-blind liraglutide (titrated to a maximum dose of 1.8mg) or placebo as add on to ongoing antidiabetic treatment.<sup>38</sup> Glycaemic control requiring reduction of insulin dose and body weight reduction were significantly better in both liraglutide-treated groups. Initial and temporary nausea and vomiting was more frequent among liraglutide treated subjects with ESKD compared with the control subjects. Using CGM, the same group showed that there is increased incidence of hypoglycaemia [3-4 mmol/L] in the liraglutide treated groups, but similar incidence of hypoglycaemia [ $<3$  mmol/L] across placebo and liraglutide treated groups.<sup>39</sup> All patients were co-administering insulin thus suggesting that the addition of liraglutide will necessitate a reduction of insulin dose which will help with weight reduction. No dose change was similarly recommended for the use of the only available oral GLP-1 receptor agonist semaglutide when used in people on mHDx. In a multicentre, open-label, multiple-dose, parallel-group trial study, once-daily oral semaglutide was found to be safe and well tolerated when was given to 11 subjects with ESKD on mHDX in comparison to 36 subjects with various degrees of renal impairment and 24 subjects with normal renal function.<sup>40</sup> The pharmacokinetics of oral semaglutide did not appear to be affected by renal impairment, thus no need for dose adjustment in people with impaired renal function.

Recent systematic reviews suggest a beneficial effect of GLP-1RAs on the risk of cardiovascular disease.<sup>41,42</sup> In a meta-analysis of eight RCTs comprising more than 60,000 patients with T2D, GLP-1 RA reduced major adverse cardiovascular events (MACE) by 14%, all-cause mortality by 12%, and hospital admission for heart failure by 11% with no increase in risk of severe hypoglycaemia, retinopathy, or pancreatic adverse effects.<sup>41</sup> In another meta-analysis, GLP-1RAs significantly reduced non-fatal stroke than SGLT-2Is.<sup>42</sup>

As people with diabetes are at high risk of cardiovascular morbidity and mortality, we suggest the use of GLP-1RA in people with diabetes who have high cardiovascular risk for their potential additional cardio protective effect.

## **Summary**

Given the very limited options available people living with diabetes should be supported and counselled for the high possibility of requiring insulin therapy,

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## **SECTION 3B INSULIN THERAPY IN PEOPLE WITH DIABETES ON DIALYSIS**

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### **RECOMMENDATIONS FOR SECTION 3B**

**3B.1** The aim of insulin therapy in people with diabetes on dialysis is to improve quality of life and avoid extremes of hypo- and hyperglycaemia. *(Grade 2C)*

**3B.2** We suggest that health care professionals (HCPs) involved in adjusting diabetes therapy review meter downloads and any point of care self-monitoring of blood glucose (SMBG) data at every diabetes related visit to optimise insulin treatment, assess variability and hypoglycaemia risk. *(Grade 2C)*

**3B.3** We suggest that HCPs should consider periodic (1-2x per year) “diagnostic” continuous glucose monitoring (CGM) analysis for all people with diabetes on dialysis on insulin treatment in order to guide future treatment planning unless they are already using Flash glucose monitoring (Flash GM) or real-time CGM systems. *(Grade 2C)*

**3B.4** We suggest that basal bolus regimes may be most flexible and best suited to the glycaemic variability (GV) seen in people with diabetes on dialysis. *(Grade 2C)*

**3B.5** We suggest that a reduction in insulin doses by 25% on haemodialysis days may reduce risk of hypoglycaemia, but assessment with CGM may offer a better guide to insulin dosing on dialysis and non-dialysis days. *(Grade 2C)*

**3B.6** We suggest that in people with diabetes on dialysis who are unable to manage a basal bolus regimen, consideration should be given to once daily regimes with longer acting insulin. *(Grade 2C)*

**3Bb.7** We suggest that if patients have troublesome hypoglycaemia on NPH insulin, conversion to analogue insulin may be considered. *(Grade 2C)*

### **AUDIT STANDARDS**

**3B.1** Proportion of people with diabetes on dialysis treated with insulin who regularly undertake SMBG and have access to HCP support to help them adjust therapy.

**3B.2 Proportion of people with diabetes on dialysis treated with insulin who have had a risk stratification for hypoglycaemia and GV risk.**

**3B.3 Proportion of people with diabetes on dialysis treated with insulin who are high risk for hypoglycaemia and GV, who have undergone Flash GM or CGM assessment over the preceding year.**

### **3B.1 Insulin in End Stage Kidney Disease (ESKD)**

Insulin is partially metabolised in the kidney.<sup>1</sup> Progressive renal impairment frequently leads to a net reduction in insulin requirement as increases in insulin resistance and reduced insulin secretion are offset by reduced renal clearance. As eGFR falls so does total insulin requirements, by around 50% when eGFR falls below 10 mL/min.<sup>2</sup>

In people with diabetes and end-stage kidney disease (ESKD), pharmacological management of glycaemia is limited by the reduced number of therapeutic options available. Indeed, frequently insulin may be the only viable therapeutic option, and whilst careful management of glycaemia with insulin is feasible, patients are at particular risk of hypoglycaemia and glycaemic variability (GV) (see SECTION 2).

In people who do not have diabetes on maintenance haemodialysis (mHDx), blood glucose tends to fall during a mHDx session with the nadir during the third hour.<sup>3,4</sup> mHDx may affect insulin secretion, clearance, and resistance as the result of periodic improvement in uraemia and acidosis. Glucose concentration in the dialysate of both mHDx and peritoneal dialysis (PD) patients may also influence glucose control, with lower glucose dialysates being associated with hypoglycemia.<sup>5</sup> It is likely therefore, that glucose control on dialysis days may be very different to that of non-dialysis days, and that therapy may need to be adjusted accordingly.<sup>6</sup>

### **3B.2 Options for insulin therapy in people with diabetes on dialysis**

The aim of glycaemic therapy in patients on diabetes should be to enhance quality of life, and reduce extremes of glycaemia. Given the increased sensitivity to insulin in dialysis patients and the risk of hypoglycaemia, a basal bolus regime with regular self-monitoring of blood glucose (SMBG) may be a safe regimen. Euglycaemic clamp studies in people with diabetes on mHDx suggest there is a 25% reduction in basal insulin requirements immediately following a mHDx session.<sup>7</sup> A reduction of basal insulin on the day of dialysis may be necessary to avoid hypoglycaemia. A recent study has suggested that a 25% reduction in insulin dose on the day of dialysis in people with diabetes on mHDx with HbA<sub>1c</sub>

<8% (64 mmol/mol) resulted in stable plasma glucose levels with fewer hypoglycaemic episodes.<sup>8</sup>

There is data to suggest that basal insulin analogues may cause less hypoglycaemia than Neutral protamine Hagedorn (NPH) insulin in people with diabetes and chronic kidney disease (CKD).<sup>9,10</sup> There is, however, little RCT data on use of insulin therapy in people with diabetes on mHDx. One small RCT suggested that converting patients from NPH or biphasic insulin to insulin glargine may improve glucose control and reduce hypoglycaemia in people with diabetes on mHDx.<sup>11</sup> Two further small studies have suggested that thrice weekly long-acting insulin at the end of dialysis in people with diabetes on mHDx improves glycaemic control significantly.<sup>12,13</sup>

Biphasic insulin regimes may be more difficult to manage on mHDx due to the irregularity of diet, glucose levels and activity imposed by mHDx sessions. Nevertheless, many people on mHDx with long standing diabetes may be on biphasic insulin regimes for some years and be reluctant to progress to basal bolus regimes. Use of CGM (as discussed in SECTION 2) may guide HCPs on insulin dose adjustment on dialysis and non-dialysis days.

Recently, the safety and efficacy of fully closed-loop insulin therapy system compared to standard insulin therapy in adults with T2D on mHDx has been undertaken in a randomised crossover trial of 26 patients.<sup>14</sup> The primary endpoint of time in target glucose range (5.6-10.0 mmol/l), showed a 15.1% improvement in the closed loop system, and time in hypoglycaemia (<3.9 mmol/l) was also reduced significantly.

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## **SECTION 4 DIETARY INTERVENTIONS FOR PEOPLE WITH DIABETES ON DIALYSIS**

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## **RECOMMENDATIONS FOR SECTION 4**

- 4.1 We recommend that the type of diabetes should be identified, and personalized dietary goals should be agreed that supports both the diabetes and renal aspects of the diet. *(Grade 1C)*
- 4.2 We recommend that each haemodialysis unit should have access to appropriate dietary expertise able to provide a holistic approach to the individual with diabetes. *(Grade 1D)*
- 4.3 We suggest that total energy should come from 50–60% carbohydrate, <30% fat and at least 15% from protein. *(Grade 2D)*
- 4.4 We recommend that individuals on maintenance haemodialysis [mHDx] achieve an energy intake of 30–40 kcal/kg ideal body weight (IBW). *(Grade 1D)*
- 4.5 We recommend that individuals on mHDx achieve a protein intake of >1.0 g/kg IBW. *(Grade 1C)*
- 4.6 We recommend that for people on mHDx with diabetes, dietary advice should be given for both dialysis and non-dialysis days to minimise significant glycaemic and caloric excursions. *(Grade 1D)*
- 4.7 We recommend that low potassium dietary restrictions are not required unless serum potassium is persistently  $\geq 6.0$  mmol/L predialysis. *(Grade 1D)*

- 4.8 We recommend that foods containing phosphate additives which have low nutrient value should be targeted prior to other high phosphate foods e.g. wholegrain products and foods with high biological value protein. *(Grade 1D)*
- 4.9 We recommend that clinicians should ensure that individuals on maintenance haemodialysis with diabetes are aware that they are more likely to be able to maintain inter-dialytic fluid gain (IDFG) at <4.5% of dry weight or <2 kg if they optimise their glucose control. *(Grade 1D)*
- 4.10 We recommend a salt intake of <5 g/day for people with diabetes on dialysis. *(Grade 1C)*
- 4.11 We recommend that all individuals with diabetes on dialysis should be screened for protein energy wasting (PEW) using a valid nutritional screening tool. *(Grade 1C)*
- 4.12 We recommend that initiation of nutrition support should be considered in those at risk of PEW; the indicators are the same in those with and without diabetes. *(Grade 1C)*
- 4.13 We recommend that individuals should receive dietary counselling and oral nutrition support as their first-line treatment if unable to meet their nutritional needs orally. Enteral or parenteral nutrition may need consideration if these interventions are insufficient. *(Grade 1D)*
- 4.14 We recommend that individuals with gastroparesis should be encouraged to have frequent small meals that are low in fat and fibre to help manage the condition. *(Grade 1C)*
- 4.15 We recommend that individuals who are being considered for a kidney transplant who are overweight/obese should be encouraged to lose weight through dietary counselling on a calorie restrictive diet, making sure protein requirements are met (1.0 g/kg IBW). *(Grade 1B)*
- 4.16 We recommend that dietary counselling should also ideally include behavioural change strategies and increased physical activity. *(Grade 1B)*
- 4.17 We recommend that all individuals with an elevated body mass index (BMI) who may not be considered for transplantation if unable to lose weight through diet, exercise and behavioural change should be considered for weight-reducing strategies including bariatric surgery. *(Grade 1C)*

**4.18 We recommend that individuals on peritoneal dialysis (PD) achieve an energy intake of 30-35kcal/kg IBW. (Grade 1D)**

**4.19 We recommend that individuals on PD achieve a minimum protein intake of 1.0-1.2g/kg IBW. (Grade 1C)**

**4.20 We recommend that calories provided through PD solutions should be estimated with caution. (Grade 1D)**

#### **4.1 Assessment and education**

It is essential to document the individual's type of diabetes and the treatment they are receiving, including dietary management, insulin (type and dose) and/or hypoglycaemic agents (type and dose). Dietary therapy for people with type 1 diabetes (T1D) or type 2 diabetes (T2D) is different and must be considered when providing dietary advice.<sup>1,2</sup>

Individuals with diabetes who progress to end stage kidney disease (ESKD) and commence dialysis may have received dietary advice from a variety of sources. Information will have come from both the diabetes and renal teams, from dietitians and from other health professionals. Priorities should include Specific, Measurable, Achievable, Relevant and Time-bound (SMART) goals that helps to achieve the lifestyle behaviour the individual wants to modify.<sup>1,2</sup>

Communication between specialties is essential to help reduce confusion and contradictory information being provided.

There is the need for holistic and individualized approach to care, addressing the needs of both diabetes and renal care. People with diabetes should have access to appropriate expertise in nutritional care and education.

#### **4.2 Energy, protein and carbohydrate recommendations for people with diabetes on maintenance haemodialysis (mHDx)**

The required energy intake is dependent on gender, age and physical factors.<sup>3-6</sup> It is important to consider the individuals ideal BMI in the context of recognized better outcomes for individuals on mHDx with higher BMI,<sup>7</sup> and maintain a BMI of at least  $>23.0 \text{ kg/m}^2$ .<sup>3,4</sup>

According to the US National Kidney Foundation Kidney Disease Outcome Quality Initiative (NKF KDOQI),<sup>2</sup> total energy intake should be:



- 50-60% from carbohydrates
- At least 15% from protein
- <30% from fat

Recommended energy intake of 30-40kcal/kg/IBW equates to approximately 50-60% of total energy from carbohydrates and >1.0g protein/kg IBW is around 15% of total energy derived from protein.

For individuals with T2D, emphasis should be placed on reducing caloric intake if overweight/obese, in addition to focusing on low glycaemic index (GI) diets and consistency in carbohydrate intake.<sup>1</sup>

The recommendation that individuals on mHDx should achieve at least a protein intake of >1.0g/kg of IBW is supported by several national and international guidelines.<sup>4,8</sup> An upper limit varies between guidance, most being expert opinion so we have not recommended an upper limit and practitioners should use their own expert judgement with an individual.<sup>4,5,8</sup>

For individuals at risk of hyper – and /or hypoglycaemia, higher levels of protein intake may need to be considered to maintain glycaemic control.<sup>3</sup>

Dietary energy intake and protein intake of people receiving mHDx are known to be lower on dialysis days than non-dialysis days.<sup>9</sup>

Carbohydrate is the primary nutritional consideration for people with T1D. All carbohydrates affect blood glucose levels and the total carbohydrate intake in a meal, or the glycaemic load is the main predictor of the rise in blood glucose levels. People with T1D on mHDx should be educated to estimate or 'count' the carbohydrate in food to be eaten and adjust the insulin dose for the meal accordingly, using individual insulin-to-carbohydrate ratios to optimize their glycaemic control.<sup>10</sup>

Education should be focused on adjusting insulin to the carbohydrate intake for individuals on multiple daily injections (MDI)/basal bolus regime or on continuous subcutaneous insulin infusion (CSII) to improve glycaemic control.<sup>1</sup>

For individuals with T1D or T2D, if they are on fixed or biphasic insulin regimens, consistency in the amount of carbohydrate at each meal, choosing low GI carbohydrates and regular eating patterns should be encouraged to prevent glucose variability and improve glucose control.<sup>1</sup>

A bedtime snack to reduce the risks of nocturnal hypoglycaemia is not routinely recommended, but a 10-20g low glycaemic index carbohydrate snack can be advised on an individual basis.<sup>1,10</sup>

### 4.3 Potassium

Potassium is found mainly in fruits, vegetables, pulses, legumes, nuts, milk, and milk products.<sup>11</sup> These foods are considered key in forming a healthy balanced diet,<sup>12</sup> with higher intakes of fruit and vegetables in haemodialysis cohorts being linked to decreased risk of cardiovascular disease (CVD),<sup>13</sup> and a reduction in mortality.<sup>14,15</sup> Fruits, vegetables, pulses, nuts, and legumes should be included in the diet in line with current “5-a-day” guidance,<sup>12</sup> and recent Kidney Disease: Improving Global Outcomes guidelines emphasise the importance of considering an individual’s whole diet rather than focusing on individual foods or nutrients.<sup>8</sup>

To prevent unnecessary restrictions and provide health benefits, a restriction in high potassium food and drinks should be avoided unless individuals have a persistent serum potassium of  $\geq 6.0$  mmol/l and only after non-dietary causes for hyperkalaemia have been excluded.<sup>16</sup>

Insulin deficiency (and therefore hyperglycaemia) causes potassium redistribution and can result in hyperkalaemia,<sup>17</sup> this additional reason for optimal glycaemic control should be emphasised and explained to the individual.

### 4.4 Phosphate

A specialist renal dietitian should carry out a dietary assessment and give individualised information and advice on dietary phosphate management,<sup>18,19</sup> to help maintain a serum phosphate towards a normal range.<sup>20</sup>

Low phosphate dietary advice has previously revolved around the reduction of animal and plant sources of phosphate such as dairy foods, eggs, seafood, and nuts. These foods, however, are also sources of protein and are essential in aiding individuals to meet their increased protein needs on dialysis.<sup>18,20</sup>

Education on reducing intake of phosphate additives such as processed meats, fish and cheeses, refined cereals, frozen potato products, cake mixes and fizzy drinks, which have high bioavailability and low nutrient value should be targeted first.<sup>8,18</sup> Advice on reducing these foods and drinks in the diet is also consistent with dietary education for individuals with diabetes.<sup>1,15</sup>

Although wholegrain products are high in phosphate, the bioavailability is lower due to the phytate content. Therefore, these foods should not be discouraged as they have a low glycaemic index and are known to be beneficial to the glycaemic control in those with T2D.<sup>1</sup>

Individuals with diabetes are advised to consume two portions of oily fish a week which are rich in omega 3 fatty acids.<sup>1</sup> Although nutritional guidance in dialysis populations does support the prescription of 1.3-4g/day omega 3 fatty acids to improve lipid profile,<sup>4</sup> care should be taken as to the frequency and quantity of oily fish consumption. This is due to its vitamin A content, which is not dialysed out and can become toxic. The high phosphate content of oily fish should also be considered and lower options such as those without bones should be advised for those requiring a low phosphate diet.<sup>4</sup>

#### **4.5 Fluid and salt**

High interdialytic fluid gains (IDFG) can negatively impact individuals receiving haemodialysis as it may result in interdialytic hypertension, intradialytic hypotension during fluid removal and associated cardiovascular disease. It can also affect an individual's capacity to conduct daily activities due to increased symptom burden including tiredness, shortness of breath and reduced mobility. To add to this, the impact of fluid overload can lead to adverse acute events and hospital admissions, sometimes requiring intensive therapy care.

Poor glycaemic control can lead to a vicious cycle of thirst and polydipsia, increasing problems with fluid management.<sup>21</sup> Therefore, an individual with poorly controlled diabetes will continue to be at risk of a higher IDFG.<sup>22</sup> In the European Best Practice Guideline, maximum IDFG is defined as 2–5 kg (4–4.5% of dry weight).<sup>3</sup> However, the European Dialysis and Transplantation Nurses Association/European Renal Care Association in 2003 defined good IDFG as 1.5–2 kg (<4% of dry weight).<sup>23</sup>

It has long been known that a high sodium intake raises blood pressure and increases the risk of stroke, CVD, and overall mortality. A low sodium intake reduces blood pressure and is associated with improved cardiovascular outcomes in those with and without kidney disease. However, limiting sodium intake may affect the taste of food and this could result in individuals being unsuccessful at such restrictions. Therefore, it is recommended that a reduction of sodium intake is of benefit to hypertension,<sup>24</sup> and recent guidance has recommended a salt intake of <5g in those with diabetes and CKD.<sup>8</sup>

The importance of reducing salt as part of fluid management should be highlighted to all individuals on dialysis.<sup>25</sup>

#### **4.6 Nutrition support**

Protein energy wasting (PEW) is a major cause of morbidity and mortality in dialysis

cohorts.<sup>4,26</sup> Studies indicate that it is more common in individuals with diabetes vs. non-diabetes undergoing mHDx,<sup>27,28</sup> although the underlying mechanisms are not fully understood. Individuals on mHDx with or without diabetes share many risk factors for PEW, such as increased nutrient losses, acidosis, inadequate nutrient intake, and increased catabolism.<sup>29</sup> There are additional risk factors for individuals with diabetes undergoing mHDx, including increased muscle protein breakdown,<sup>30</sup> increased co-morbidities and a higher prevalence of gastroparesis.<sup>31</sup> It is essential to investigate causes of reduced oral intake and identify strategies to overcome these.

Although there is much guidance on the prevention and treatment of muscle wasting for people on dialysis,<sup>5</sup> there is little specific to those with diabetes. It seems intuitive that some approaches would remain the same such as ensuring adequate energy and protein intake and optimizing dialysis prescription. However, additional measures may need to be considered such as the impact of nutritional interventions on glycaemic control, though this is less relevant in individuals with malnutrition,<sup>32</sup> and can usually be managed pharmacologically.

### **Nutritional screening**

All inpatients should be screened for PEW on admission to hospital and weekly thereafter.<sup>5,33</sup> Commonly used nutrition screening tools may not identify all individuals at risk of PEW given fluid fluctuations. Therefore, it has also been recommended that outpatients should be screened at their first clinic appointment and/or at initiation of dialysis and 3–6 monthly thereafter.<sup>5</sup> Resources may not allow for this frequency of screening on all dialysis units, and a clear referral pathway or criteria should be in place to identify those at risk of PEW.<sup>5</sup>

Current guidelines indicate that nutrition support should be considered in individuals with one or more of:

- BMI <20 kg/m<sup>2</sup>.<sup>29,34</sup>
- Unintentional non-oedema weight loss >5–10% over 3–6 months.<sup>34</sup>
- Subjective global assessment graded B/C or 1–5.<sup>4</sup>
- Intercurrent catabolic acute conditions which render normal nutrition impossible, or which prevent adequate oral intake.<sup>34</sup>

Accelerated loss of lean body mass with no changes to BMI and body weight have been observed in individuals with diabetes on mHDx,<sup>30</sup> suggesting that anthropometric markers to estimate muscle mass should additionally be used in individuals with diabetes, such as

handgrip strength.<sup>4</sup> Bioimpedance or preferably multi-frequency bioelectrical impedance (MF-BIA) is recommended to assess body composition where available.<sup>4</sup>

### **Dietetic management of nutrition support**

Individuals at risk of malnutrition should receive dietary counselling to discuss how to increase the calorie and protein content of their diets.<sup>3</sup> This may be through the use of diet and/or oral nutritional supplements (ONS). If intake is insufficient despite the use of ONS,<sup>3,5</sup> nasogastric feeding or gastrostomy feeding for long-term use could be considered.

A US national survey of 181,196 subjects found that individuals with renal failure had a 1.6-fold increased risk of mortality post percutaneous endoscopic gastrostomy (PEG) placement.<sup>35</sup> Careful consideration should be given when assessing suitability for a PEG.

Currently, when intensive dietary counselling, ONS and enteral feeding have failed, a course of intra-dialytic parenteral nutrition (IDPN) can be considered in people on mHDx.<sup>4,5,34</sup> Although IDPN has been shown to improve energy and protein balance and nutritional parameters, it has not been shown to improve survival.<sup>36</sup> Special attention is required in individuals with diabetes receiving IDPN including careful blood sugar monitoring.<sup>37</sup>

European Best Practice Guidelines recommend products specifically formulated for people on dialysis, which are appropriate in relation to fluid and electrolytes.<sup>3</sup> There are no specific recommendations for those with diabetes. It is important that individuals are educated on the carbohydrate load of supplements so that they can make appropriate changes to insulin doses and timing of supplements to limit effects on glycaemic control.

### **Gastroparesis**

Gastroparesis is a serious complication of diabetes that may develop at least 10 years after diabetes diagnosis and is defined as delayed gastric emptying without any mechanical obstruction in the stomach.<sup>38,39</sup> Gastric emptying is significantly delayed in dialysis cohorts compared to control and this can affect nutritional status.<sup>39</sup> Gastric stasis can cause nausea, vomiting and dyspeptic symptoms such as early satiety, fullness or postprandial discomfort and bloating as well as anorexia.<sup>39</sup> These symptoms may lead to inadequate nutritional intake and add to the difficulty in controlling blood glucose. The aim of dietetic management is to maintain nutritional status as well as improve glycaemic control.

A suitable diet for the individual with gastroparesis is small, frequent, low in fibre and fat. A smaller meal size may help to reduce gastric emptying time although meal size should be individualized according to tolerance. For individuals with gastroparesis requiring enteral feeding, a nasojejunal tube or jejunostomy would be appropriate.<sup>40</sup>

## 4.7 Obesity

There are virtually no standards, guidelines, or studies with regards to obesity in individuals with diabetes on dialysis. There has been more research on obesity and haemodialysis, and we can presume that a significant proportion of these individuals would have diabetes.

Advice in relation to obesity within the dialysis population is complicated, as some research results suggest that obesity is positively correlated with survival of individuals on dialysis, i.e. a higher BMI predicts a lower mortality rate.<sup>41</sup> This is known as the obesity paradox, and may in part be explained by the fact that individuals on mHDx with an elevated BMI demonstrate a better nutritional status,<sup>42</sup> whereas PEW is considered to be a major cause of morbidity and mortality in haemodialysis cohorts.<sup>4,26</sup> Observations that high creatinine concentrations before haemodialysis treatment are a predictor of survival may be explained by the fact that they are also the direct consequence of increased muscle mass and a higher dietary protein intake.<sup>7</sup>

Although there is a substantial amount of data that support a protective role for obesity, some authors question the existence of the obesity paradox. They suggest that obese individuals are protected in the short term, but later are susceptible to higher mortality risks than people of normal body weight.<sup>43</sup>

ESKD is ideally treated with renal transplantation and obesity contributes to increased risk of morbidity following surgery due to higher risk of co-morbidities such as cardiac, respiratory, and metabolic diseases.<sup>44</sup> For obese individuals on dialysis treatment who are eligible for kidney transplantation, weight loss is advised to reduce obesity-related surgical complications and improve graft survival after transplantation. The British Transplantation Society guidelines suggest that obese individuals with BMI >30 kg/m<sup>2</sup> present technical difficulties and are at increased risk of post-operative problems and therefore should be screened rigorously for cardiovascular disease.<sup>45</sup>

## **Weight reducing diets**

Little research has been done on specific diets and weight reduction in individuals on dialysis and the diet most successful in aiding weight loss in people with T2D is still under debate. Guidelines for obesity in T2D suggest that for overweight and obese individuals the focus should be on total energy intake depending on the individual's diet rather than the source of energy in the diet for optimal glycaemic control and weight reduction.<sup>1,46-48</sup> Guidelines recommend energy restriction to induce 5-7% weight loss in overweight/obese individuals with diabetes and dietary considerations should include moderate fat intake (<35% energy total energy intake) and reducing saturated fat intake (<10% total energy intake).<sup>1</sup>

One non-randomised trial following a 2-year weight management program using low fat, exercise and orlistat demonstrated significant weight loss in individuals on dialysis who were to undergo transplantation.<sup>49</sup> To our knowledge there are no other studies on this in the literature. There has been no study examining the use of low carbohydrate ketogenic diets in obesity and dialysis, and it is suggested a high protein diet may be a significant source of uraemic toxins and phosphate, which would be detrimental to health in the renal population.

For obese individuals who are not considered transplant candidates the benefits of weight loss remain uncertain.<sup>50</sup>

## **Weight loss medications and bariatric surgery**

The NICE guideline on 'Weight management: lifestyle services for overweight or obese adults' states that pharmacological treatment should be considered for people who have not reached their target weight loss or have plateaued on diet, activity and behavioural changes.<sup>51</sup>

During a systematic review,<sup>52</sup> only five studies evaluated pharmacologic therapy alone or combined with another intervention, and only two of these studies included individuals on dialysis. Both studies involved a two-year structured weight loss programme that included using orlistat, a calorie-restricted diet and aerobic exercise and individuals in both achieved weight loss.<sup>49,53</sup>

While GLP-1 receptor agonists have been approved for the treatment of obesity in the general population, the lack of experience and evidence for their use in subjects with renal failure means they cannot presently be recommended in this population, but this is an option that requires investigation.

As the prevalence of obesity in the dialysis population is increasing,<sup>54</sup> more individuals are being considered for bariatric surgery within the dialysis population; however, very limited data have been published with regards to bariatric surgery in CKD and especially individuals on dialysis. Reviews have found bariatric surgery reduced BMI or body weight in all studies (changes in BMI ranged from  $-4.5 \text{ kg/m}^2$  to  $-20.8 \text{ kg/m}^2$ ) and this was the most effective intervention for achieving long lasting weight loss in morbidly obese individuals with CKD.<sup>52</sup>

A systematic review warns of the additional risk associated with bariatric procedures in people with CKD and the need for careful monitoring of fluid intake, kidney function and dialysis access.<sup>52</sup> They suggest large prospective controlled studies are needed to provide insights into safety and effectiveness of bariatric procedures in this population.

#### **4.8 Considerations for peritoneal dialysis**

Individuals treated with peritoneal dialysis (PD) with a lower BMI have a higher risk of mortality.<sup>55,56</sup> It is therefore vital that they consistently meet their nutritional needs to avoid protein energy malnutrition. However, monitoring should also prevent excessive weight gain with increases in visceral fat and muscle loss.

Current guidelines advise that individuals require a minimum of 1.0-1.2 g/kg IBW per day of protein to maintain a stable nutritional status and take account of protein losses during peritoneal dialysis.<sup>4,6,57</sup> For individuals at risk of hyper- and/or hypoglycaemia, higher levels of dietary protein intake may also support better glycaemic control.<sup>4</sup>

An individual's protein intake should be considered in conjunction with adequate energy intake,<sup>58</sup> as in situations of an energy deficit from carbohydrate or lipid sources, protein is degraded to meet metabolic energy demands. Current advised energy requirements are 30-35 kcal/kg of IBW which is less than haemodialysis requirements to account for the calories provided by glucose in the dialysis solutions.<sup>4,57</sup> Information regarding glucose intake from different PD solutions are described in Table 6.1 of this guideline.

The amount of glucose absorbed will depend on peritoneal membrane transport characteristics, dwell time, dialysate volume, and the individual's blood glucose.<sup>59</sup> For individuals on continuous ambulatory peritoneal dialysis (CAPD) with normal peritoneal transport capacity, it has been estimated that up to 60-80% of the daily dialysate glucose load is absorbed; potentially adding up to 100-200 grams/24 hour (400-800kcal/day).<sup>60,61</sup> The caloric intake from shorter automated PD dwells is estimated to be lower at 40–50%.<sup>62</sup>

Not only can the glucose contribute to total energy intake, it may also be detrimental to glycaemic control. Therefore glucose-free solutions (Icodextrin or Amino acids) can be



considered.<sup>63</sup> It should be noted that Icodextrin is a starch derived glucose polymer and absorbed in low quantities (20-40%) even after long dwells (8-12hrs).<sup>64</sup> Therefore, the calorie contribution from Icodextrin should be considered negligible.

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## **SECTION 5A MANAGEMENT OF HYPOGLYCAEMIA IN PEOPLE WITH DIABETES ON DIALYSIS**

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### **RECOMMENDATIONS FOR SECTION 5A**

#### **For people on active treatment of diabetes with insulin:**

**5A.1** We recommend that where there is a pre-dialysis glucose of  $<7$  mmol/L, 20–30 g low glycaemic index carbohydrate is provided at the beginning of the haemodialysis session to prevent further decline of blood glucose level. (*Grade 1D*)

**5A.2** We recommend that capillary glucose should be assessed pre- and post-haemodialysis. (*Grade 1D*)

**5A.3** We suggest that the dialysis unit should ensure a hypoglycaemia treatment is always accessible to patients, including during travelling to and from the dialysis unit. (*Grade 2D*)

#### **In cases of hypoglycaemia**

**5A.4** We recommend that an appropriate rapid-acting carbohydrate treatment should be provided to take into account fluid, potassium and phosphate restrictions. (*Grade 1D*)

**5A.5** After treatment initiation, glucose level should be checked 15 minutes after the treatment is given. If not above 4 mmol/L, a repeat dose of the 15 g rapid glucose followed by 10–20 g complex or low glycaemic index carbohydrate is recommended. (*Grade 1C*)

**5A.6** We recommend that patients and staff should be educated in regard to the appropriate treatment of mild to moderate hypoglycaemia and hypoglycaemia unawareness. (*Grade 1D*)

#### **5A.1 Recognising hypoglycaemia**

Hypoglycaemia is the medical term for low blood glucose, and is defined as a blood glucose level of  $<4$ mmol/L.

- Mild hypoglycaemia is defined as an episode of hypoglycaemia which can be managed by the individual themselves.

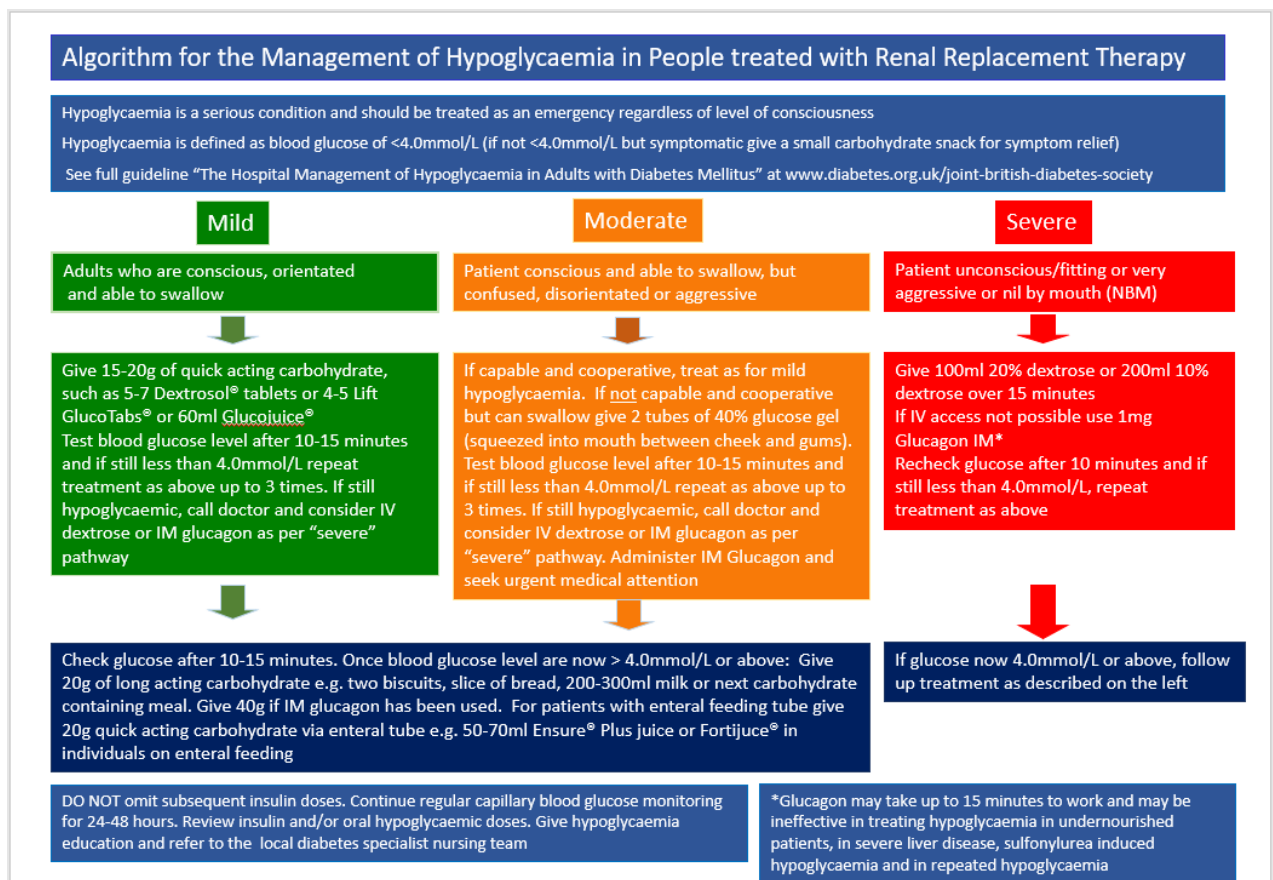


- Severe hypoglycaemia is defined as an episode of hypoglycaemia which requires assistance from another individual.

People on dialysis are at risk of hypoglycaemia. Blood glucose levels tend to decline during a haemodialysis session with the lowest glucose being before the third hour even though no hypoglycaemia may be reported.<sup>1</sup> Mean glucose concentrations post haemodialysis are also found to be significantly lower on dialysis vs. non-dialysis days,<sup>2</sup> and 75% of hypoglycaemic events occur within 24 hours of dialysis.<sup>3</sup>

A dietary intake of 10–20 g of a low GI carbohydrate is recommended at the second hour of haemodialysis to prevent further decline of blood glucose level at the third hour. Fruit juice is not recommended because of its high potassium content. It is important to monitor pre- and post-haemodialysis blood glucose levels. If the pre-haemodialysis blood glucose level is <7 mmol/L, it is recommended to take 20–30 g carbohydrate is given at the beginning of haemodialysis. It is recognized that individuals given a large amount of food on dialysis have an increased incidence of hypotension during the 3rd and 4th hours due to increased blood flow to the intestines.

**Fig. 5A.1 JBDS recommendations on managing hypoglycaemia.**<sup>4</sup>



The treatment of hypoglycaemia in the inpatient/dialysis setting should be based on national guidance issued by the JBDS (Fig. 5A.1).<sup>4</sup> For people who are experiencing hypoglycaemia symptoms even when the blood glucose level is above 4mmol/L. The Joint British Diabetes Societies recommends an intake of 15–20 g of carbohydrate, such as 1 medium slice of bread or 2 digestive biscuits (Table 5A.1).<sup>4</sup>

*Table 5A.1 Examples of low GI sources of carbohydrate providing 10 g of glucose<sup>4</sup>*

- 1 Digestive biscuit
- 1 Hobnob biscuit
- 2 Rich Tea biscuits
- 2 Cream crackers
- 1 Shortbread
- 1 small apple
- 1 small pear
- 2 small satsumas
- 1 thin slice bread
- ½ crumpet

The blood glucose level post-haemodialysis needs to be considered to ensure it is safe for the person to go home with minimum risk of hypoglycaemia. However, there is no specific guidance as to the amount of carbohydrate recommended to prevent post-dialysis hypoglycaemia. Therefore, it is recommended to ensure a hypoglycaemia treatment is always accessible to the individual, including during travelling to and from the dialysis unit.

## **5A.2 Treating an episode of hypoglycaemia**

Many of the rapid acting glucose preparations recommended for treating hypoglycaemia can be inappropriate for people with diabetes on maintenance haemodialysis (mHDx) (e.g. 150 mL fruit juice or 100 mL cola drink). Not only do these treatments contribute toward significant fluid intake, especially the person is anuric and following 500 mL daily fluid restriction, but they also contain high potassium (fruit juice) and phosphate (cola) content. Table 2 shows recommended hypoglycaemia treatment for patients with hyperkalaemia, hyperphosphataemia and anuria:

**TABLE 5A.2 RECOMMENDED HYPOGLYCAEMIA TREATMENTS**

<b>Source of rapid carbohydrate</b>	<b>Amount to provide approximately 15G of carbohydrate</b>
Lift (Glucojuice)	60mL
Lift (Glucotabs)	5
Dextro-Energy tablets	6
Jelly Babies	5

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## **SECTION 5B FOOTCARE**

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## **RECOMMENDATIONS FOR SECTION 5B**

**5B.1 We recommend that all people with diabetes on dialysis should be considered high risk of developing foot ulcers and are at high risk of amputation. (Grade 1B)**

**5B.2 We recommend that all people with diabetes on dialysis should inspect their feet daily and if they are unable to do this because of poor eyesight or frailty their carers should be advised to undertake this for them. (Grade 1C)**

**5B.3 We recommend that the heels of all people with diabetes on maintenance haemodialysis [mHDx] should be protected with a suitable pressure relieving device during haemodialysis. (Grade 1C)**

**5B.4 We recommend that all people with diabetes on dialysis should have regular podiatry review. (Grade 1C)**

**5B.5 We recommend that all people with diabetes on dialysis should have their feet screened monthly using a locally agreed tool and by competent staff on the dialysis unit. (Grade 1C)**

**5B.6 We recommend that if the individual has an ulcer or there is any other concern the patient should be referred to the diabetic foot team within one working day and each dialysis unit should ensure that there is a clearly defined escalation pathway for these individuals. (Grade 1B)**

**5B.7 If the individual is on home dialysis we suggest it is the responsibility of the clinician in charge of their care to ensure that they have an annual foot review and are attending review by the foot protection team. (Grade 2B)**

**5B.8 We recommend that any individual presenting with a hot swollen foot should be referred to the diabetic foot team within 24 hours. (Grade 1B)**

End stage kidney disease (ESKD) and chronic kidney disease (CKD) stages 4–5 are independent risk factors for diabetic foot disease, with associated neuropathy, peripheral arterial disease (PAD) and delayed wound healing. Dialysis is independently associated with a >4-fold risk of foot ulceration (odds ratio [OR], 4.2 [1.7–10]),<sup>1-4</sup> and the risk of the development of a foot ulcer is temporally related to the onset of renal replacement therapy.<sup>5</sup> One study has shown that only 5% of all people with diabetes on dialysis, independent of ethnicity, had no apparent risk factors for foot ulceration (either neuropathy, PAD or past foot ulcer).<sup>6</sup> Neuropathy greatly increases the risk of pressure related ulcers, particularly on the heels of recumbent patients. Care must be taken to ensure adequate pressure relief in renal dialysis units when the individual is recumbent for prolonged periods of time.<sup>7</sup>

A study using UK General Practice data has shown that major amputations are 7–8 times more likely in people with diabetes and eGFR <30 mL/min compared with those with eGFR >60 mL/min.<sup>1</sup> In one study from the USA people with diabetes on dialysis who had had a lower extremity amputation were almost twice as likely to have had a major amputation compared with a cohort of people with diabetes who had no CKD.<sup>8</sup> Ten year post-operative mortality was 3.9-fold higher among dialysis patients compared with those without CKD; the highest mortality being amongst those who had above knee amputations.<sup>8</sup> People with diabetes and ESKD are also significantly less likely to ambulate post major amputation.<sup>9</sup>

Podiatry input on dialysis units reduces the frequency of development and severity of diabetic foot complications among people with diabetes on peritoneal and maintenance haemodialysis (mHDx),<sup>10,11</sup> and it is recommended that regular podiatry assessment (at least 3 monthly) is ensured for this high risk group.<sup>12</sup> This may need to be on dialysis units for those on mHDx as this frail, multi-morbid population may have difficulty accessing community podiatry appointments.<sup>4</sup>

Daily self-foot checking is recommended by Diabetes UK for those assessed at high risk of developing foot disease such as those with ESKD and on dialysis.<sup>13</sup> Given the difficulty many people with diabetes, particularly those with other co-morbidities, have in being able to see all areas of their feet and given the very high risk of limb loss in this population, it has been suggested that additional foot checks be done on the dialysis unit for those on mHDx. Indeed, monthly intradialytic foot checks implemented at one large haemodialysis facility in the USA resulted in a 17% decrease in major amputations.<sup>14</sup>

Charcot foot (Charcot neuropathic osteoarthropathy) is associated with very high morbidity and is frequently misdiagnosed as infection or venous thrombosis, or particularly in people with renal disease, as gout. The diagnosis is often, therefore, delayed which is associated

with worsening structural damage, secondary ulceration, osteomyelitis and potentially avoidable limb loss.<sup>15</sup>

The risk of the development of an acute Charcot foot also associates with renal disease – in one series, 30% were on renal replacement therapy.<sup>16</sup> This may simply be because neuropathy and nephropathy are both microvascular complications of diabetes. However, the reduced hydroxylation of vitamin D and the hyperparathyroidism of advancing renal failure may make expression of the disease more likely by their impact on bone strength.

The recommended treatment of an acute Charcot foot is offloading in a non-removable cast or walker.<sup>12,17</sup> However, people on dialysis may tolerate this poorly due to changing peripheral oedema. Other methods of offloading (for example removable cast and wheelchair use) may be required.

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## **SECTION 5C RETINOPATHY IN PEOPLE WITH DIABETES ON DIALYSIS**

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### **RECOMMENDATIONS FOR SECTION 5C**

**5C.1 We recommend that all people with diabetes on dialysis should be asked about when they last had retinal screening as part of their annual review. Ideally, this should have occurred within six months prior to starting dialysis in order to ensure that those who have severe non proliferative retinopathy, proliferative retinopathy or macular oedema have been referred for treatment ideally before initiating dialysis.**

*(Grade 1C)*

**5C.2 We recommend the implementation of the UK Kidney Association guidelines on management of glycaemia, hypertension, lipids and anaemia in people with diabetes on dialysis in order to reduce the risk of progression of retinopathy after starting dialysis. (Grade 1C)**

**5C.3 We suggest that in those individuals identified as having severe macular or retinal disease extra care is taken to minimise intradialytic hypotension and rapid change in BP or fluid status during haemodialysis. (Grade 2D)**

**5C.4 We recommend continuing with anti-coagulation and anti-platelets therapies when indicated in patients with diabetic retinopathy on dialysis. (Grade 1C)**

**5C.5 We recommend prompt control of hypertension in patients with diabetic retinopathy on dialysis following initiation or maximisation of erythropoietin therapy. (Grade 1C)**

**5C.6 We suggest the use of angiotensin convertase inhibitors (ACEIs) and angiotensin 2 receptor blocker (ARBs) to treat hypertension in patients with diabetic retinopathy on dialysis. (Grade 2B)**

**5C.7 We recommend that if people with diabetes on dialysis experience acute changes to their vision, they should be referred urgently to a hospital eye service for an urgent assessment and that each dialysis unit should have an escalation pathway for such individuals**

## 5C.1 Introduction

Diabetic retinopathy (DR) is a microvascular complication of type 1 (T1D) and type 2 diabetes (T2D) and is commonly present in people with diabetic nephropathy. It is the most common cause of visual loss among adults worldwide.<sup>1</sup> DR is progressive from mild to severe non-proliferative retinopathy characterised by haemorrhages, exudates and micro aneurysms, to proliferative diabetic retinopathy (PDR) characterised by neovascularisation, vitreous haemorrhages and retinal detachment. Macular oedema and loss of central vision, characterised by retinal thickening, can develop at all stages of DR.<sup>2</sup>

Risk factors associated with DR include duration of diabetes and glycaemic control,<sup>3</sup> hypertension,<sup>4,5</sup> and dyslipidaemia.<sup>5,6</sup> Randomised controlled trials (RCTs) have shown that intensive glycaemic control can prevent or delay the onset and progression of DR,<sup>7-11</sup> as can lowering blood pressure,<sup>11-14</sup> and optimising serum lipids.<sup>15-18</sup>

The 2021 American Diabetes Association,<sup>19</sup> and UK consensus working group and the Royal College of Ophthalmology,<sup>2</sup> recommend that optimisation of glycaemia, control of blood pressure and serum lipids should be undertaken to reduce the risk of development or progression of DR.

To our knowledge there are no specific UK, European or American guidelines on management of retinopathy in people with diabetes on dialysis. The impact of dialysis on DR and better understanding of risk factors for progression of DR for people with diabetes on dialysis needs further study. This is particularly important in order to improve the quality of life of people with diabetes on dialysis especially given the improvement in their life expectancy that has been reported.<sup>20</sup>

## 5C.2 Natural history of DR in end-stage kidney disease (ESKD)

People with diabetes who reach end stage kidney disease (ESKD) commonly have DR. Early studies suggested that the majority of people with diabetes who reach ESKD would have developed DR by the time they start dialysis, with blindness affecting between 23-50% by the time they start dialysis.<sup>21,22</sup>

There has been concern that the use of heparin on maintenance haemodialysis (mHDx) and rapid fluid shifts to correct hypervolaemia causing sudden changes in blood glucose or blood pressure, leading to deterioration of DR or sight loss after the initiation of dialysis. It is also thought that rapid changes in blood pressure with hypotensive and hypertensive episodes that can occur on dialysis can increase the risk of vitreous bleeding or retinal detachment.<sup>23</sup> Progression of retinopathy is reported in people with diabetes treated with mHDx.<sup>24,25</sup> In

contrast, however, several other studies showed that retinopathy stabilised or improved in the majority of patients after starting mHDx.<sup>21,26-28</sup> Preservation or improvement of sight was also reported after starting peritoneal dialysis (PD).<sup>29,30</sup> Analysis of risk factors that lead to progression of retinopathy after commencing mHDx suggest that in 50%, unstable blood pressure was correlated with progression but found no evidence to suggest that retinopathy was accelerated by dialysis.<sup>31</sup>

The effect of dialysis on the status of diabetic macular oedema (DME) is controversial. DME results from the hyperpermeability of retinal vessels. Intravitreal injection of anti-vascular endothelium growth factor (anti-VEGF) agents have become the gold standard in the treatment of DME. Some studies suggest no effect mHDx on macular leakage.<sup>32,33</sup> Other studies, however, suggest a benefit of mHDx on DME with disappearance of hard exudates after dialysis.<sup>34-36</sup>

In a retrospective study using Optical Coherence Tomography (OCT), the incidence of any macular oedema one month before and after commencement of dialysis in 26 eyes of 15 patients found that after initiation of dialysis, the incidence of DME decreased from 69% to 26.9% without any ocular treatment.<sup>37</sup> The investigators attributed this to improvement in uraemia and fluid overload. In a retrospective multicentre study of 70 subjects and 132 eyes, initiation of mHDx resulted in improvement in DME especially in those with the sub retinal detachment type and those with best central visual acuity (BCVA).<sup>38</sup> The investigators showed that nearly 95% of eyes did not require anti-VEGF injections during the year after commencement of mHDx. They reported that central retinal thickness (CRT) was significantly reduced at one month after initiation of mHDx, and concluded that initiation of mHDx may be effective to treat DME refractory to anti-VEGF therapy. They recommended that mHDx should not be delayed, but initiated in those with DME with poor BCVA and refractory to anti-VEGF therapy. A further prospective study has shown that mHDx has a positive impact on macular oedema.<sup>39</sup> This study assessed macular thickness in 36 subjects with diabetes and ESKD 60 minutes before and after a haemodialysis session using OCT, and found that mHDx resulted in a decrease of macular thickness.

Formal assessment of retinal and macular disease before starting dialysis is necessary to ensure preservation of sight and maintenance of the patients' quality of life.

### **5C.3 Anaemia and the use of erythropoietin (EPO) in DR**

Anaemia is associated with the development and progression of small vessel disease in diabetes. Therefore, treating anaemia with EPO has been the subject of interest to treat microvascular disease in people with diabetes on dialysis.

Early studies suggested that early diagnosis and treatment of anaemia may decrease the risk of progression of DR. In both the UKPDS 50<sup>40</sup> and ETDR<sup>41</sup> studies, anaemia was observed to be an independent risk factor for development of DR and severe visual loss. Several studies have been designed to evaluate the association of DR and haemoglobin (Hb) levels in people with diabetes without significant renal dysfunction and a number of studies have shown an association between DR and anaemia. In a cross sectional study of 1691 people with diabetes in Finland (not including ESKD) a twofold increased risk of retinopathy was seen in those with Hb less than 12g/dl.<sup>42</sup> In a further prospective cross sectional study of 1100 people with diabetes, low Hb level was found to be a risk factor for development and severity of DR, and people with anaemia were 2.4 times more likely to develop DR.<sup>43</sup> In another study of 426 subjects with diabetes with 17 years follow up, a direct relationship between Hb level and the development or deterioration of PDR was demonstrated.<sup>44</sup> One study suggested that Hb level was the only factor that showed a significant inverse association with the severity of DR and retinal ischemia.<sup>45</sup> A more recent cross section study of 2123 Korean patients with T2D with no ESKD, a 19% decrease in DR risk was found per 1.0g/dl increase in Hb level.<sup>46</sup> The occurrence of DR may also have an association with serum iron and only serum iron had a significantly inverse relationship with the presence of DR.<sup>47</sup> All of these studies were undertaken in non-dialysed people with CKD, and showed an association between anaemia and DR, but did not provide evidence of a direct role of anaemia in the development or progression of DR.

There have been small studies suggesting that treating anaemia in people with diabetes may be associated with improving DR.<sup>48-50</sup> One report described a series of five people with diabetes and CKD, in which treatment with EPO was correlated with substantial resolution of macular hard exudates.<sup>48</sup> A further report has described three cases of people with diabetes who rapidly developed high-risk PDR associated with severe anaemia, in whom DR stabilised with treatment of the anaemia.<sup>49</sup> One study suggested that treating anaemia to a target Hb above 12.5g/dl was associated with improving ischaemia in the diabetic retina.<sup>50</sup>

The main concern with EPO therapy is worsening of hypertension, vascular access thrombosis and potential for cardiac events.<sup>51,52</sup> Current guidelines from the UK Kidney Association recommend a target Hb in patients with CKD and anaemia receiving EPO of 10-12g/dl.<sup>53</sup> Current evidence does not support aiming for higher Hb levels in people with diabetes on dialysis who have DR.

#### **5C.4 Use of heparin or aspirin in DR**

mHDx requires the use of anti-coagulation, which may increase the risk of vitreous haemorrhage (VH). Prospective study, however, has not suggested increased risk of VH in people with DR treated with PD, mHDx or those with functioning renal transplants.<sup>54</sup> In a single centre retrospective, controlled study, there was no significant increase in VH in the first year between the mHDx and PD groups and the incidence of VH in the dialysis period was significantly lower than in the pre dialysis period.<sup>55</sup>

Aspirin in the 'Early Treatment Diabetic Retinopathy Study' (ETDRS) was found to have no beneficial effect on DR progression or loss of visual acuity in individuals with DME or severe non-proliferative DR during nine years of follow and that aspirin treatment was not associated with an increased rate of vitrectomy.<sup>56,57</sup> A smaller RCT evaluating aspirin alone and in combination with dipyridamole reported a reduction in microaneurysms on fluorescein angiograms in both groups as compared with placebo.<sup>58</sup>

Based on these findings, there appears to be no contraindication to aspirin or heparin use in people with DR on dialysis.

#### **5C.5 Does renin-angiotensin system blockade have any role in preventing DR?**

The renin–angiotensin system (RAS) has been found to be upregulated in retinopathy,<sup>59</sup> and the vitreous activity of ACE was found to correlate with the increased vitreous level of VEGF in the eyes of people with diabetes and proliferative diabetic retinopathy.<sup>60</sup>

ACE inhibitors (ACEI) and angiotensin-II receptor blockers (ARBs) appear to reduce the incidence and progression of retinopathy in normotensive people with T1D with no nephropathy.<sup>61-64</sup>

ACEIs and ARBs are effective in treating hypertension in people with diabetes on dialysis.<sup>65-67</sup> It is not clear, however, whether these drugs reduce DR in people with diabetes on dialysis.

#### **5C.6 Conclusions**

The above discussion suggests it is unclear whether initiation of dialysis is a risk factor for worsening of retinopathy. Clinicians should ensure that people with diabetes starting dialysis have undergone a recent retinal screening to stage and treat pre-existing DR to reduce the risk of blindness. Urgent eye examination to those who have "crash landed" on dialysis or who have been lost to follow up is indicated to ensure safe commencement of dialysis.

Future research in people with DR on dialysis needs to be conducted in order to understand how dialysis affects DR, and establish evidence-based therapies to prevent progression and/or restore vision.

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## **SECTION 5D DIABETIC KETOACIDOSIS IN PEOPLE ON DIALYSIS**

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## **RECOMMENDATIONS FOR SECTION 5D**

### **Recognising Diabetic Ketoacidosis on the haemodialysis unit**

**5D.1 We suggest that every haemodialysis unit should have point of care blood ketone testing available and staff should be trained in its use. (Grade 2D)**

**5D.2 People with diabetes on maintenance haemodialysis [mHDx] should have their blood ketones checked using point of care testing kits if they have:**

- **Type 2 diabetes (T2D and their pre-dialysis or post-dialysis capillary blood glucose (CBG) is persistently raised above 15.0 mmol/L (2 consecutive readings taken an hour apart) and they have symptoms suggestive of DKA OR**
- **Type 1 diabetes (T1D) and have CBG above 15.0 mmol/L. (See Table 1.1 for when to test for ketones). (Grade 2D)**

**5D.3 If blood ketones are above 3.0 mmol/L, the person should have access to personnel and facilities to enable rapid and appropriate assessment and management of Diabetic Ketoacidosis (DKA). (Grade 2D).**

**5D.4 We suggest there should be a pathway in place at each haemodialysis unit for the rapid and safe prescription and administration of a bolus dose of insulin for use in an emergency. (Grade 2D)**

**5D.5 If there is a delay in transfer to a facility for intravenous insulin infusion, we suggest the following (Grade 2C):**

- d) Administration of subcutaneous bolus dose of short acting insulin at a dose of 0.05unit/kg**
- e) Hourly monitoring of CBG and blood ketones**
- f) Clear documentation of the administered dose and timing of insulin bolus and handing this information over to the receiving team when the patient is transferred.**

## **Diagnosing Diabetic Ketoacidosis**

**5D.6** We suggest that the diagnostic criteria for DKA in people with ESKD are the same as for adults with preserved renal function (See Table 1.2). (*Grade 2C*)

## **Managing Diabetic Ketoacidosis**

**5D.7** After DKA has been diagnosed, treatment should follow the JBDS DKA Guidelines update June 2021 (See Table 1.3) Paying particular attention to the fluid replacement regimen recommended for those on dialysis. (*Grade 2D*)

## **Audit Recommendations for Section 5D**

**5D.1** All people with T2D and on maintenance haemodialysis with CBG > 15 mmol/L (on 2 consecutive readings taken 1 hour apart) and symptoms of DKA have their blood ketones tested.

**5D.2** All people with T1D and on maintenance haemodialysis with CBG > 15 mmol/L have their blood ketones tested.

## **5D.1 Introduction**

Diabetic Ketoacidosis (DKA) is less common in people with end-stage kidney disease (ESKD) than in people with preserved renal function. Deteriorating renal function offsets poor glycaemic control by a reduction in renal gluconeogenesis, changes in insulin catabolism and a reduction in insulin clearance.<sup>1</sup> An osmotic diuresis rarely occurs in oligo-anuric ESKD patients, consequently protecting them from dehydration. Although rare, DKA does happen in people with ESKD.<sup>2</sup> Due to the complex physiology, limited evidence and variation in local service infrastructure, the management can be challenging. In this review we will be focussing on the potential for a person with diabetes on mHDx to present with DKA to their haemodialysis unit and the issues that the haemodialysis unit need to be aware of in order to best manage these individuals. There are considerable differences between individual haemodialysis units in regards to their level of medical cover and in relation to their links to an acute medical hospital. An example escalation pathway for the diagnosis for DKA is available in the Appendix (see Appendix 1).

## **5D.2 Recognising DKA on the haemodialysis unit**

DKA can occur in both Type 1 and Type 2 diabetes (T1D and T2D). People with ESKD who are diagnosed with DKA have lengthier hospital stays and are at an increased risk of hospital readmissions.<sup>2</sup> Recognising DKA is important as patients can be critically unwell

and frequent contact with healthcare professionals on the haemodialysis unit offers opportunities to identify DKA promptly. NICE CKS Guidance classifies significant hyperglycaemia as having CBG above 11.0 mmol/L,<sup>3</sup> and suggests that ketones should be checked if CBG is above 11.0 mmol/L and the patient has clinical features suggesting DKA. For people with T1D, JBDS recommendation is that anyone with CBG above 14.0 mmol/L should have their ketones checked regardless of symptoms.<sup>4</sup> However, a large observational study demonstrates that hyperglycaemia may be more profound in people with ESKD than those with preserved renal function.<sup>5</sup> Hence, we suggest a higher cut-off CBG of above 15.0 mmol/L for measuring ketones. It is therefore important that dialysis staff clarify the diabetes classification (T1D or T2D) of each individual with diabetes when they commence dialysis in the unit. To reduce unnecessary ketone testing, we suggest testing in T2D only if the individual is both symptomatic and has CBG above 15 mmol/L on two consecutive readings taken one hour apart. Dialysis unit staff should be aware of the symptoms of DKA (see below). This guidance will be reviewed through audit process and adjusted as more information about DKA incidence is ascertained.

**Table 5D.1. Suspect DKA and test for ketones:**<sup>3-5</sup>

If T2D, CBG > 15.0 mmol/L (on 2 separate readings taken an hour apart) and symptoms suggestive of DKA
If T1D, CBG > 15.0 mmol/L and asymptomatic

### **Symptoms suggestive of DKA**

When assessing people with raised CBG, it is important to recognise the difference between those who feel well, and those who have non-specific symptoms that may be due to DKA. Observational studies do not show any significant difference in prevalence of symptoms between DKA in T1D and T2D with preserved renal function.<sup>6,7</sup> There is no evidence of asymptomatic DKA in T2D in ESKD. Symptoms that may be suggestive of DKA include nausea/vomiting, confusion, abdominal pain, drowsiness and fruity smell on breath.<sup>3</sup> These symptoms may be mild and easy to miss. Deep sighing respiration (Kussmaul breathing) is a sign of respiratory compensation of metabolic acidosis in people with preserved renal function, but those on maintenance haemodialysis may not always present with this, as haemodialysis may partially or fully mitigate the metabolic acidosis. Signs of severe dehydration may also not be present as the lack of an osmotic diuresis may protect against fluid loss. It is important to be aware that individuals may miss dialysis sessions due to these

non-specific symptoms and equally, missed dialysis sessions may contribute to worsening of these symptoms.

### 5D.3 Diagnosing DKA in people on haemodialysis

Observational data found no significant difference in pH or bicarbonate levels in DKA between those with ESKD and those with preserved renal function.<sup>5</sup> Therefore, we recommend that the diagnostic criteria of DKA in ESKD are the same as for adults with preserved renal function (Table 5D.2). While overall  $\beta$ -hydroxybutyrate ketones levels were lower in ESKD than in people with preserved renal function,  $\beta$ -hydroxybutyrate above 3.0 mmol/L has a diagnostic sensitivity of 86% and specificity of 69% for bicarbonate less than <15.0 mmol/L.<sup>5</sup> Therefore, we suggest that capillary ketones above 3.0 mmol/L should prompt immediate medical assessment.<sup>8</sup>

**Table 5D.2** Diagnosis of DKA.<sup>9</sup>

<u>Measurement</u>	<u>Parameter</u>
Capillary Blood Glucose	>11.0 mmol/L or known DM
Blood Ketones	>3.0 mmol/L
Venous Bicarbonate OR pH	<15.0 mmol/L <7.3

Whilst some haemodialysis units may have access to point of care blood gas testing, it may not be available at all units, and although there is a high probability that a person on haemodialysis has acidaemia (especially pre-dialysis), it is likely that the individual will need to be transferred for medical assessment after CBG/Ketone testing to confirm a diagnosis of DKA. Although anion gap may help with diagnosis and assessing severity in people with preserved renal function,<sup>9,10</sup> we suggest that anion gap is not taken into consideration when diagnosing DKA in ESKD, as it is likely to be raised due to raised urea.

### 5D.4 Managing DKA in people on haemodialysis

The management of DKA in people on haemodialysis needs to be tailored in response to each individual, taking into consideration physiological changes that occur with ESKD. As there are no randomised controlled trials to guide care, suggestions and recommendations

for management are based on very limited evidence in the form of case reports, observational data and expert opinion.

It may be possible to diagnose and initiate medical treatment on the haemodialysis unit in some cases where point of care blood gas testing is available, however timely transfer to an acute hospital environment (Emergency Department/ Medical Assessment Unit/ Diabetes or Renal Ward/ Level 2 or 3 environment) is suggested for further management and closer monitoring. Prompt initiation of DKA treatment after diagnosis is recommended; if there is a risk of delay in initiation of fixed rate insulin infusion (FRII), we suggest that 0.05unit/kg bolus insulin is administered subcutaneously. We recognise that this is different from the JBDS DKA guideline update, which recommends that a bolus intramuscular (IM) dose of insulin 0.1 unit/kg be administered in people with preserved renal function.<sup>9</sup> This is because, although IM has a faster rate of absorption than SC in people with preserved renal function, the pharmacokinetic and pharmacodynamic profile of IM insulin in ESKD is poorly understood.<sup>11</sup> Additionally, IM route should be avoided in people on dialysis who receive systemic anticoagulation at the start of the dialysis session. Therefore, we suggest that on balance, a bolus subcutaneous insulin dose is given, with close hourly CBG monitoring, and the time and dose administered is documented clearly and handed over when the patient transfers. People with DKA and ESKD have higher risk of hypoglycaemia (OR 3.3, 95% CI [1.51-7.21]),<sup>5</sup> therefore it is recommended that the dose of bolus insulin be reduced by 50% to 0.05 unit/kg to reduce the risk of hypoglycaemia.<sup>12,13</sup> If there is a high clinical suspicion of DKA, those with hyperglycaemia and ketosis should be treated with the above to ensure patient safety until a diagnosis of DKA can be confirmed, despite the possibility that partial treatment may complicate the diagnosis at a later stage. It is recognised that haemodialysis units may have different accessibility to medications such as insulin and availability of a prescriber on site. Therefore, we suggest that each unit has a pathway in place for obtaining a prescription for insulin. Short acting insulin should also be made available at each dialysis unit for use in emergency situations such as above.

The JBDS June 2021 DKA guidelines update recently been updated to include a section on those with ESKD, see link: <https://abcd.care/resource/management-diabetic-ketoacidosis-dka-adults>.<sup>9</sup> (Accessed 09.02.23) Management following transfer to an acute hospital setting needs to be tailored to each individual to reduce the risk of pulmonary oedema,<sup>2</sup> and hypoglycaemia,<sup>2,14</sup> as per the JBDS DKA guidelines update (see Table 5D.3).



**Table 5D.3. Key highlights of JBDS DKA Guidelines June 2021 Update.<sup>9</sup>**

- If rate of glucose reduction is more than 3.0 mmol/L/hr or glucose falls below 14.0 mmol/L, consider a lower rate of insulin infusion to reduce the risk of hypoglycaemia
- Potassium supplementation is not usually required – in cases of hyperkalaemia, consider early involvement of critical care or renal team for consideration of haemodialysis
- Carefully assess fluid status and consider small (250 mL) boluses of fluids with frequent reassessment to avoid fluid overload.

Due to changes in glucose homeostasis and insulin resistance during and after haemodialysis, capillary blood glucose should be carefully monitored,<sup>15,16</sup> and adjustment of insulin infusion during haemodialysis and the period after should be considered to reduce the variability in glycaemic control during haemodialysis. It is vital that underlying causes of DKA, such as sepsis are identified and promptly treated in order to reduce morbidity and mortality in this population.<sup>9</sup>

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## **SECTION 5E END OF LIFE CARE IN PEOPLE WITH DIABETES ON DIALYSIS**

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### **RECOMMENDATIONS FOR SECTION 5E**

**5E.1 People with diabetes on dialysis approaching end of life or where a palliative care pathway has been agreed should be managed in accordance with Trend Diabetes End of Life clinical care recommendations for people with diabetes. Treatment and interventions should be focussed on symptoms. (Grade 1D)**

Deciding to withdraw from renal replacement therapy is recognised as a common cause of death in US and UK patients. This is more common in older people, those with chronic or progressive co morbidities and people who are becoming increasingly frail.<sup>1</sup>

Care provision and links with other specialist teams, including palliative care teams, is warranted at this time.<sup>2</sup> Clear guidance for the management of end of life care in individuals deciding to withdraw from renal replacement therapy is essential in order to support teams and carers during what is a difficult time for all. A coexisting diagnosis of diabetes can often add to the complexity of care planning required for end of life management.

Diabetes management needs to be included when planning care for these individuals. Diabetes medications including insulin treatment may need to be reduced or even stopped in some individuals with Type 2 diabetes (T2D) so that hypoglycaemia can be avoided. Conversely it is important that insulin treatment is not stopped completely in people with Type 1 diabetes (T1D), as this can lead to diabetic ketoacidosis (DKA ) and severe dehydration. Early liaison with the diabetes specialist team is recommended when planning care for these individuals.

Blood glucose monitoring can be minimised to only once daily with a glycaemic target of 6–15 mmol/L without diabetes symptoms, in those receiving insulin treatment. This is only used to rule out hypoglycaemia, hyperosmolar hyperglycaemic state or DKA. The giving of fluids either by mouth or other methods is entirely the choice of the individual or if there is lack of capacity, the carer. Teams need to ensure that the individual's wishes are paramount when planning end of life care and that there is effective communication with the individual, their relatives or carers and GP.<sup>2,3</sup>

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## **SECTION 6 MANAGEMENT OF DIABETES IN PEOPLE UNDERGOING PERITONEAL DIALYSIS – CLINICAL CONSIDERATIONS AND PRACTICE POINTS**

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### **PRACTICE POINTS FOR SECTION 6**

- 6.1 HbA<sub>1c</sub>, despite its limitations in persons with renal disease, is currently recommended as the preferred marker to assess long term glycaemic control in people with diabetes on PD.**
- 6.3 Other markers such as GA or fructosamine may be less reliable than HbA<sub>1c</sub> in PD.**
- 6.3 HbA<sub>1c</sub> treatment goals and targets should be individualized and other clinical parameters such as anaemia, erythropoietin treatment and PD regime have to be considered when managing diabetes in people on PD.**
- 6.4 Avoid the use of GDH-PQQ based glucometers or strips as these can give rise to falsely elevated BG readings in people undergoing PD with Icodextrin. This can result in the risk of excessive insulin treatment and iatrogenic hypoglycaemia.**
- 6.5 An individualised approach with consideration of risks of hypoglycaemia, type of PD and glucose content of dialysate is required.**
- 6.6 Specialist input of the multidisciplinary diabetes team is required for high-risk people with diabetes on PD such as people with T1D, people on insulin with risk of hypoglycaemia, people with high glycaemic variability, people with recent hospital admissions with hypo/hyperglycaemic emergencies and people who have not received structured diabetes education within the last one year. (see Section 2)**

**6.7 All people with diabetes on PD should receive education on the risk of hypoglycaemia, advice on mitigating risks and guidance on self-management**

**6.8 For people with diabetes on PD requiring insulin treatment we advise the use of insulin subcutaneously only.**

**6.9 We do not recommend intraperitoneal administration of insulin due to the lack of efficacy data and the known risks.**

**6.10 If using glucose-based dialysates there may be a need for increased insulin doses to counter the systemic absorption of glucose from the dialysate.**

**6.11 Exact insulin titrations and regimens should be individualized. A standard MDI or CSII (in T1D) may be preferred as it gives more flexibility towards dose titrations.**

### **6.1 Introduction to section**

The aim of this section is to provide a summary of clinical considerations and practical aspects of management of diabetes in people undergoing peritoneal dialysis (PD). A systematic review was not able to be conducted due to the lack of sufficient and suitable clinical studies. Due to this dearth of evidence to support management decisions, we have developed a series of clinical practice points to guide and inform clinicians looking after people with diabetes on peritoneal dialysis (PD) rather than making explicit recommendations. Practice points represent the expert judgment of the writing group and may also be based on limited evidence. Unlike recommendations, practice points are not graded for strength of recommendation or quality of evidence.

In reviewing the literature evidence, a literature search was conducted using PubMed, MEDLINE, Central, Google Scholar and ClinicalTrials.gov., from 1980 through to September 2021. The search was limited to publications in English. Due to the limited availability of clinical trials related PD in this patient population, all systematic reviews, meta-analysis, prospective observational studies of cross-sectional, case control, longitudinal cohort design or randomized studies and case series were included.

### **6.2 Introduction to PD**

Peritoneal dialysis utilises the peritoneum as a semi-permeable dialysis membrane through which solutes and fluid can be exchanged between capillary blood and the instilled dialysate. Continuous ambulatory PD (CAPD) usually consists of 2 or 3 day time exchanges and a longer night time exchange, whilst automated PD (APD) consists of multiple shorter exchanges performed at night by an automated cycling machine and a longer day time exchange. A significant minority of people have a day or two off PD each week. All treatment

is conducted by the person on PD or their caregiver outside of the hospital environment. As a home therapy, PD offers many advantages to the person with kidney failure in terms of autonomy and independence compared with in-centre haemodialysis.

For successful PD, in addition to the removal of electrolytes and solutes we also need to enable trans-capillary ultrafiltration (UF) of water from the capillaries into the peritoneal cavity which requires the establishment of an osmotic gradient.

In general, PD solutions constitute of one of three osmotic agents; glucose, icodextrin or amino acids.

### **Glucose containing PD solutions**

Glucose remains the most commonly used osmotic agent in peritoneal dialysate. Standard solutions available in the UK have concentrations ranging from 1.36% to 3.86% (as described below). Despite its small molecular size and consequent net reflection coefficient of ~0.03 it still has significant osmotic potential due to the presence of ultra-small, water-only pores (AQP-1) in the peritoneal membrane. The deleterious effects of conventional glucose based dialysate on the structure and function of the peritoneal membrane itself have been well documented.<sup>1</sup> However, as a result of its small molecular size glucose is freely absorbed from the peritoneal cavity, this results in loss of the osmotic gradient and net absorption of glucose estimated at 100-300g per 24 hours depending on the PD regime.<sup>1</sup> PD prescription reflects principles described in international guidelines, but an important component is ensuring sufficient ultrafiltration.<sup>2</sup> Stronger glucose solutions have greater osmotic gradients and thereby greater ultrafiltration.

### **Icodextrin 7.5%**

Osmosis can also be induced with colloidal agents; the most commonly used clinically is Icodextrin. Icodextrin is a mixture of starch-derived high molecular weight (1,638-45,00kDa) glucose polymers, with a structure similar to that of glycogen. Icodextrin is metabolized to oligosaccharides including maltose, maltotriose and maltotetraose.<sup>3</sup> Any absorption from the peritoneal cavity is predominantly through the lymphatic circulation. Unlike glucose, it has a net reflection coefficient approaching one, and therefore provides an almost constant colloid osmotic pressure, able to sustain ultrafiltration for up to 16 hours even in fast transporters.<sup>4</sup> Icodextrin is currently only licensed for a single exchange daily, and due to its sustained ultrafiltration properties, it is best suited to the long exchange, but there is increasing experience with two exchanges daily when indicated.

## Amino acids

The other commercially available non glucose based dialysate contains a 1.1% solution of amino acids. This solution provides similar ultrafiltration potential to 1.36% glucose based dialysate but has the advantage of no exposure to absorbed glucose or glucose degradation products. It is mainly used when there is a worry about nutritional status but its use is limited to a single daily exchange, and this is only used occasionally, because of concerns regarding the potential for symptomatic uraemia and acidosis, and lack of robust evidence of meaningful patient benefit.

## Types of PD solutions used in the UK

The PD solutions currently being used in the UK for CAPD and APD are marketed by Baxter Healthcare and Fresenius Medical Care.

The following table summarizes the selected products by Baxter Healthcare and Fresenius medical care being used for PD along with key composition and colour coding (where available). There are solutions available nationally and internationally and it is out of scope of this work to provide an exhaustive list of all PD solutions.

**Table 6.1 – Types of PD solutions with composition and colour coding.** (Sources - <https://www.baxterhealthcare.co.uk>, <http://www.freseniusmedicalcare.co.uk/healthcare-professionals/spcpil-downloads>) Accessed 09.02.23

Manufacturer	Product	Composition	System	Colour code
Baxter healthcare	PHYSIONEAL (1.36%)	1.36% Glucose	Separate solutions for CAPD and APD (2L)	Yellow
	PHYSIONEAL (2.27%)	2.27% Glucose	Separate solutions for CAPD and APD (2L)	Green
	PHYSIONEAL 40 (3.86%) APD Solution	3.86% Glucose	APD (2L)	Orange



	DIANEAL 1.36%	1.36% Glucose	Separate solutions for CAPD (1.5, 2, 2.5L) and APD (2.5L, 5L)	Yellow
	DIANEAL 2.27%	2.27% Glucose	Separate solutions for CAPD (1.5L, 2L) and APD (2.5L, 5L)	Green
	DIANEAL (3.86%)	3.86% Glucose	APD	Orange
	EXTRANEAL	7.5% Icodextrin	Separate solutions for APD (2L, 2.5L) and CAPD (2L, 2.5L)	Purple
	NUTRINEAL	1.1% Amino Acid	Separate solutions for APD (2.5L) and CAPD (2L)	Blue
Fresenius medical care	All available with Calcium 1.25 or 1.75 mmol/l  Balance 1.5% glucose  Balance 2.3% glucose  Balance 4.25% glucose		stay•safe system – for CAPD  sleep•safe system – for APD  Safe•Lock system – for APD	None

	All available with Calcium 1.25 or 1.75 mmol/l  BicaVera 1.5 % Glucose  BicaVera 2.3% glucose  BicaVera 4.25% glucose	Double-chamber bag  stay safe system  sleep safe system  sleep safe combo:	None
	CAPD/DPCA 17 (Glucose 83.2 mmol/L – 15.0 g anhydrous glucose, up to 0.75 g fructose)  CAPD/DPCA 18 (Glucose 235.8 mmol/l- 42.5 g anhydrous glucose, 2.1 g fructose)  CAPD/DPCA 19 (Glucose 126.1 mmol/l- 22.73 g anhydrous glucose, up to 1.1 g fructose)	CAPD: stay•safe bag  APD): sleep•safe bag	None

### 6.3 Monitoring of glycaemic control in people with diabetes on PD

The criteria and types of tests for diagnosis of type 1 and type 2 diabetes (T1D and T2D) are described in detail in recent guidelines.<sup>5</sup> However, for many of the tests that should be utilised for diagnosis of diabetes, the absorption of dialysate constituents merits specific consideration in people with ESKD who are undergoing PD.

Both random and fasting plasma glucose (FPG) should be interpreted in the context of the peritoneal glucose. FPG can be effectively used for diagnosis of diabetes in these patients as demonstrated by multiple studies,<sup>6,7</sup> although the dialysate glucose load has been shown to affect the circulating random glucose levels.<sup>8</sup> The impact of either Icodextrin- or amino acid-based dialysate is not clear but theoretically should have little impact. The test is therefore ideally performed in the absence of intra-peritoneal dialysate, but if this is considered inappropriate, use of an Icodextrin dialysate long dwell may be a reasonable compromise.

An oral glucose tolerance test (OGTT) with 75g oral glucose is a useful test to diagnose diabetes in people with FPG 5.1-7 mmol/L.<sup>9</sup> However, the OGTT is also potentially affected by dialysate glucose absorption. It should ideally be performed with no dialysate present, but failing that, using an Icodextrin based dialysate, or timing the test for the end of a long dwell with a low or medium glucose strength solution would be advisable. As FPG is often maintained in the normal range or sometimes reduced as a result of decreased renal clearance of insulin in people with ESKD,<sup>10</sup> hyperglycaemia can be often predominantly post prandial, which can be successfully detected through OGTT.<sup>11</sup>

#### **6.4 Assessing long term glycaemic control**

The same limitations for the use of HbA<sub>1c</sub> in ESKD failure apply to people on PD (see SECTION 2). Glycated albumin (GA) and fructosamine are alternatives to HbA<sub>1c</sub> to assess long term glycaemic control. While glycated albumin has no interferences from above factors affecting HbA<sub>1c</sub>, studies have shown that this can be unreliable in CKD patients with hypoalbuminaemia. Hypoalbuminaemia is more prevalent in PD than HD as a result of protein losses into the dialysate and possibly better preserved residual urine output and proteinuria. HbA<sub>1c</sub> can be considered as a better indicator of overall glycaemic control than GA.<sup>12,13</sup>

The Glycaemic Indices in Dialysis Evaluation (GIDE) Study in 2015 assessed different parameters including HbA<sub>1c</sub>, GA and fructosamine and the baseline data suggested that these patients need individualised diabetes monitoring taking all the factors into consideration.<sup>14,15</sup> Moreover, it is important to keep in mind that none of these indices will give an idea about glycaemic variability.

#### **6.5 Assessing glycaemic variability**

##### ***Self-monitoring of capillary blood glucose (SMBG) in people with diabetes on PD***

Self-monitoring of capillary blood glucose (SMBG) is the most commonly used method to assess day to day glycaemic control in the majority of the people with diabetes. Different types of glucometers and strips are being used for this purpose. Ideally capillary blood glucose (CBG) should be monitored 6-8 times/day in order to gain a better idea about glycaemic variability.

A major clinical consideration is that false readings depending on the type of glucometer being used, can occur in people with diabetes on PD. There are multiple clinical case reports

of significant hypoglycaemia due to falsely elevated readings promoting inappropriate insulin administration<sup>16,17</sup>

In general, there are 2 key components of a glucometer: an enzyme reaction and a detector. Three types of enzymatic reactions are currently being utilized: glucose oxidase, glucose dehydrogenase (GDH), and hexokinase<sup>18</sup> GDH based glucometers use 3 types of co-enzymes, namely; GDH and co-enzyme pyrroloquinoline-quinone (GDH-PQQ), GDH and co-enzyme nicotinic adenine dinucleotide (GDH-NAD) and GDH and co-enzyme flavin adenine dinucleotide (GDH-FAD). These have different characteristics and different associations with interfering substances.

Icodextrin is metabolized to maltose which cross reacts as glucose, giving falsely high glucometer values when using GDH-PQQ based glucometers. This overestimation of BG can lead to significant hypoglycaemia and delay in recognizing hypoglycaemia.<sup>19-21</sup>

Therefore, in order to avoid over estimation of blood glucose levels and subsequent over treatment with insulin, **GDH-PQQ based glucometer systems should not be used in people undergoing PD**. For additional patient safety, it is recommended to review labels of both the glucose meter and the test strips used or if doubtful, to contact the manufacturers to ensure the type of method being used.

It is important to note that maltose metabolites generated during PD with Icodextrin take at least two weeks to return to baseline, and therefore, the glucometer assay interference may persist for some time after cessation of Icodextrin usage.<sup>20</sup>

In addition, Glucose Oxidase based glucometers/ strips can have assay interference in patients with anaemia with low haematocrit. (see SECTION 2)

More details about the country specific glucose monitor list and the type of enzymatic method being used can be obtained from [www.glucozesafety.com](http://www.glucozesafety.com).

(<https://www.glucozesafety.com/uk/pdf/Glucose%20Monitor%20List%20UK.pdf>) Accessed 09.02.23

Of the glucose monitor brands currently available in the UK, Accu-Chek Go/Go S System and Accu-Chek Integra System (Roche Diagnostics) utilize the GDH-PQQ based method hence should not be used in people undergoing PD, especially with Icodextrin.

Other limitations of SMBG which apply to all people with diabetes include inability to assess the trend of glucose variability and failure to identify nocturnal or asymptomatic hypoglycaemia.

## Practice points

Avoid the use of GDH-PQQ based glucometers or strips as these can give rise to falsely elevated BG readings in people undergoing PD with Icodextrin. This can result in the risk of excessive insulin treatment and iatrogenic hypoglycaemia.

## Intermittently scanned and real time continuous glucose monitoring (rtCGM)

Flash and real time CGM are effective technologies to assess overall glycaemic control and glycaemic variability. These technologies provide added advantages of being able to assess the glycaemic variability throughout the day, asymptomatic hypoglycaemia and hyperglycaemia. Please see relevant guidance on this in section 2 for detailed descriptions.

With regards to accuracy, PD patients are not subject to the rapid fluid shifts associated with haemodialysis but there are other PD specific issues which may impact reliability. As discussed above Icodextrin significantly alters the reliability of GDH-PQQ based assays and there remains uncertainty as to the impact of dialysate solutions on the other enzymatic systems such as the glucose oxidase method most commonly used in these systems.<sup>22,23</sup> To date, there are no reports or studies that have described the effect of Icodextrin on flash or real time CGM systems.

CGMs have previously been used in studies with small patient numbers to demonstrate markedly different patterns of glycaemia in patients with similar HbA<sub>1c</sub> values, underappreciated levels of hypoglycaemia and improved glycaemic variability associated with glucose sparing regimes.<sup>24</sup> However, there are no studies looking at the impact of CGMs on glycaemic control in PD patients. Consequently, the accuracy and utility of CGMs in PD populations needs further evaluation.

Intermittently scanned or real time CGMs are not licensed or validated to be used in persons with PD in the UK. However, clinical experience suggests that these may be helpful to titrate insulin in order to minimise glycaemic variability and hypoglycaemia in this high-risk population. In our opinion, Flash GM or CGM may have a role in all people with diabetes on PD who are on insulin treatment.

## 6.6 Metabolic impact of PD

While the glucose-based solutions have been used for a long time and demonstrated to be safe, effective and inexpensive, the downside is that the solutions can lead to systemic

absorption of glucose and cause hyperglycaemia and high variability requiring increased insulin levels. Glucose is absorbed from the dialysate into the blood along a concentration gradient. As the glucose concentration in the dialysate is higher than that in blood,<sup>25</sup> this can increase plasma glucose levels and other components of metabolic syndrome.<sup>8,26</sup> The amount of glucose absorbed will depend on the tonicity and volume of the dialysate, transport characteristics of the peritoneal membrane, dwell time and the patient's blood glucose level.<sup>6</sup>

The amount of glucose absorbed per day from dialysate was first studied in the 1980s. At this point it was viewed as a potentially positive side effect of PD in 'under-nourished' dialysis patients.<sup>27</sup> Subsequently data on the high prevalence of hyperglycaemia, insulin resistance and cardiovascular disease in PD cohorts has raised concerns about the additional metabolic risk posed by PD treatment. The relative contribution of peritoneally absorbed glucose compared with the myriad other cardiovascular, nutritional and metabolic risk factors these people are exposed to remains debated.

Commencing PD has been associated with new onset hyperglycaemia and impaired glucose tolerance.<sup>9,28</sup> Advanced age, increased baseline body mass index, increased dialysate glucose load and ongoing systemic and intra-peritoneal inflammation have been identified as potential risk factors for the development of new onset diabetes or impaired glucose tolerance in people starting on PD.<sup>6,9</sup> However, epidemiological studies assessing the risk of new onset diabetes mellitus in people on PD compared to their haemodialysis counterparts have produced conflicting results.<sup>29-32</sup> Assessment of the impact of peritoneally absorbed glucose on short-term and long-term glycaemic control is compounded by issues around accuracy of diagnosis and monitoring in this population as described above.

## **6.7 Treatment of diabetes in people on PD**

In general, management of diabetes in people with diabetes on PD should be based on the currently available standard guidelines on management of diabetes in ESKD (see Section 3). The main objective of treatment of people with diabetes on PD should be to maintain euglycemia during the dwell time, to prevent post prandial hyperglycaemia and to avoid morning hypoglycaemia.<sup>33</sup>

### **1. Oral anti diabetic drugs (OAD) and GLP-1 receptor agonists**

Please refer to Section 3 on general guidance of utilising oral hypoglycaemic agents and injectables in people with CKD and ESKD. There are limited data on OADs in PD. In clinical practice several OAD's such as metformin and sulfonylureas are contraindicated and not

recommended for use in kidney failure. Similarly, there are no data on the use of GLP-1 receptor agonists in people with diabetes on PD and we would not recommend the use of this class. SGLT2 inhibitors have been found to have cardiorenal benefits in people with CKD, however, they have no glycaemic benefit in people on dialysis. In the opinion of the writing group, DPP-4 inhibitors can be used in PD with appropriate dose adjustments as per their individual medication license.

## **2. Insulin**

The renal clearance of insulin reduces drastically when eGFR is <15-20 mL/min. Furthermore, insulin clearance in non-renal tissues such as liver and muscle is also impaired in kidney failure, leading to prolonged half-life of insulin.

It is well known that insulin resistance increases in people with kidney failure due to multiple mechanisms including inflammation and oxidative stress.<sup>34</sup> However, both HD and PD are known to improve insulin resistance.<sup>35</sup> Some studies have demonstrated an improvement of insulin sensitivity in those on PD compared to HD.<sup>36</sup> However, any improvement in insulin sensitivity may be counteracted by exposure to high glucose containing peritoneal dialysate.<sup>25,27</sup>

Initial strategies to mitigate against the extra glucose load included the use of intraperitoneally administered insulin. Whilst there was evidence that this route of administration may improve glycaemic control,<sup>37</sup> it was subsequently noted that it had adverse effects on the lipid profile, predisposed to hepatic subcapsular steatosis and increased the risk of peritonitis.<sup>38-40</sup> Consequently, this is no longer recommended.

There are limited published guidelines or studies regarding the insulin dose titrations in people with diabetes on PD. Persons on PD with glucose-based dialysates may need increased insulin doses to counter the systemic absorption of glucose through the dialysate, taking the pattern of dialysate prescription into account where possible. In particular, APD will have most glucose absorption overnight, whilst CAPD will be primarily during the day.

Previous studies have found that the daily glucose load from dialysate is a factor determining the need for increased insulin doses. A single centre study in Hong Kong published in 2007 assessed the insulin requirement in 60 Chinese patients with T2D (treated with insulin) and diabetes nephropathy, newly initiated on PD. The PD regimen in general remained stable in these patients through the six month review period. This study demonstrated that the insulin requirement during the first six months of PD directly correlated with the daily glucose load. PD patients treated with a standard regimen of 1.5% 2 litre exchange thrice daily often did not require increases in insulin dosage. However, a daily exchange of 2.5% dialysate would require an additional 4 units of SC insulin per day.<sup>33</sup> In contrast, an observational study

conducted in Germany, published in 2002, involving both HD and PD patients with T1D with both SC and IP insulin routes demonstrated a reduction in SC insulin requirement at the start of dialysis.<sup>37</sup>

### **Clinical considerations when using insulin treatment in people with diabetes on PD**

Insulin dose adjustments should always be individualised. In the opinion of the writing group for people with diabetes requiring insulin who are on PD, a multiple daily injection (MDI) regime with long-acting analogue insulin (ideally given in the morning) and pre-meal rapid acting insulin is preferred. This approach is less likely to cause hypoglycaemia and can enable more flexible dose adjustment to help mitigate glycaemic variability related to glucose load in dialysate as compared to a twice daily premixed insulin regime.

We would advise moving basal insulin to breakfast in people on CAPD. Quick acting insulin (e.g. Novorapid® or Humalog®) may be required if high glucose levels (>15 mmol/L) are noted after each exchange. In people on APD, consider moving basal insulin to night-time. In patients on APD, a dose of pre-mixed 70/30 or 75/25 insulin can be considered at the start of the dialysis session to cover the excessive glucose load if a multiple daily injection regime is not feasible.<sup>10</sup>

People with diabetes on PD and particularly those treated with insulin or hypoglycaemia inducing agents require education on avoiding hypoglycaemia and management of hypoglycaemia should this occur. We recommend regular reinforcement of this advice and guidance by the diabetes multidisciplinary team. We recommend that appropriate treatment for hypoglycaemia be kept within close proximity should they require treatment.

If there is a change from glucose based dialysate to non-glucose based dialysate such as Icodextrin, reduced insulin doses may be required to avoid subsequent hypoglycaemia. Any change to the glucose concentration of the PD prescription should be discussed with the diabetes team so that the insulin doses can be appropriately adjusted. People on PD being transferred to HD, will require dose adjustments of insulin to avoid hypoglycaemia due to sudden withdrawal of the glucose containing PD regime.

There are no clinical trials or large case series of people with T1D on MDI therapy or Continuous Subcutaneous Insulin Infusion (CSII) with an external pump on PD. In general, increased basal rates especially overnight, to counter the increased glucose load, as well as adjustments to insulin-to-carbohydrate ratios to avoid post prandial hyperglycaemia will be required. Similarly, a reduction in basal rates or basal insulin dose if on MDI is required after any reduction of the glucose concentration of the dialysate, in order to avoid hypoglycaemia. Closed loop systems would be a better way forward in optimising the diabetes management



of in people with T1D and kidney failure with promising data reported in people on haemodialysis. However, studies are needed to evaluate the use of such systems in people with diabetes on PD.

### **Adjustments to the dialysis prescription- impact on metabolic parameters and diabetes**

As currently available international guidelines on cardiometabolic issues in PD do not focus in detail on specific issues for people with diabetes on PD, these will be dealt with here.<sup>41</sup>

The role for adaptation of the dialysis prescription in improving glycaemic control in people with diabetes on PD remains debated. There is no strong evidence for choosing one PD modality (APD versus CAPD) over another with regards to glycaemic control.

Glucose based solutions remain the most commonly used, however as discussed above, they are associated with significant systemic absorption of glucose. Alternative osmotic agents such as Icodextrin and amino acids were developed in an attempt to circumnavigate some of the drawbacks of traditional glucose-based solutions.

The combined results of two large, multi-national, interventional studies (IMPENDIA and EDEN) in people with diabetes on PD demonstrated the potential systemic benefits of reduced dialysate glucose exposure.<sup>19</sup> During a six month study period participants were randomised to treatment with either a glucose sparing regime (using Icodextrin and amino-acid based dialysate for two of the daily exchanges) or the control group who undertook standard all-glucose based dialysate. In an intention to treat analysis, HbA<sub>1c</sub> fell in the intervention group but remained unchanged in the control group (0.5% difference between groups, 95% CI 0.1% to 0.8% p=0.006). The separation between the two groups was observed as early as 3 months and persisted to the six month study end point. This corresponded with a reduction in VLDL cholesterol and serum triglycerides in the intervention group. This study reported a statistically significant difference in the number of serious adverse events in the intervention group compared to controls. These were predominantly cardiovascular (hypertensive crisis and fluid overload) and infectious although none of the infectious complications were deemed by investigators to be related to the study solution there were more adverse events in the intervention group especially uncontrolled hypertension and fluid overload. It has been suggested that this was the result of overzealous glucose minimisation at the expense of fluid balance.

The results of a recent systematic review and meta-analysis of studies including people both with and without diabetes, enriched with previously unpublished data do not support the use of a single daily Icodextrin exchange alone as a strategy for improving glycaemic control.<sup>42</sup> This analysis of 19 RCTs, comparing Icodextrin for the long dwell versus glucose only

solutions reported no difference in fasting plasma glucose or HbA<sub>1c</sub> between groups despite a reduction in glucose exposure and absorption equivalent to 45g per day. Any glucose lowering potential may have been diluted by the inclusion of people without diabetes. A meta-analysis including only people with diabetes is ongoing. In apparent contrast to the IMPENDIA/EDEN results, this review and the preceding Cochrane review report significantly lower rates of uncontrolled fluid overload in the group prescribed a daily Icodextrin exchange.<sup>43</sup>

Icodextrin in combination with an amino acid solution as part of a glucose minimising regime (as seen in IMPENDIA/EDEN) can result in improved glycaemic control although this may be at the expense of fluid balance. On the other hand, icodextrin in isolation has strong evidence of a beneficial impact on fluid status,<sup>42,43</sup> suggesting that a focus on glucose minimisation without sufficient regard to fluid balance was the driver of this outcome. There is now evidence that single exchange icodextrin may reduce mortality,<sup>42</sup> but without strong evidence that a single icodextrin exchange daily improves glycaemic control, the apparent benefits may be via improved fluid balance. In people with diabetes on PD it is reasonable to use icodextrin for the long exchange with the aim of reduced glucose exposure and improved ultrafiltration. Regimes aimed at further glucose minimisation have the potential to improve glycaemic control; however, this should never be at the expense of maintaining fluid balance.

A glucose sparing regime comprised of both icodextrin and amino acid solutions resulted in improved glycaemic control however there is no strong evidence that a single amino acid exchange alone results in better glycaemic control.

There are several glucose sparing osmotic agents such as taurine, polyglycerol, carnitine and xylitol, that are currently in the preclinical research stage.<sup>43</sup> Their impact on glycaemic control is yet to be determined. The pros and cons of using icodextrin in diabetes patients on PD are summarized in Table 2.

Advantages	Disadvantages
Reduced glucose absorption through dialysate leading to reduced insulin requirements	Dilutional hyponatraemia due to absorption of metabolites such as maltose
Improved glycaemic variability and HbA <sub>1c</sub> when used as part of a glucose minimisation regime	Recommended for only 1 exchange over a 24 hour period

Possible modest improvement of triglycerides, VLDL, and apolipoprotein B

False readings with certain types of glucometers (see above) and resultant risk of hypoglycaemia

**Table 6.2 – Advantages and disadvantages in using Icodextrin based PD solution as an alternative to glucose-based PD solutions**

**Personal experience of having diabetes and being on PD treatment**

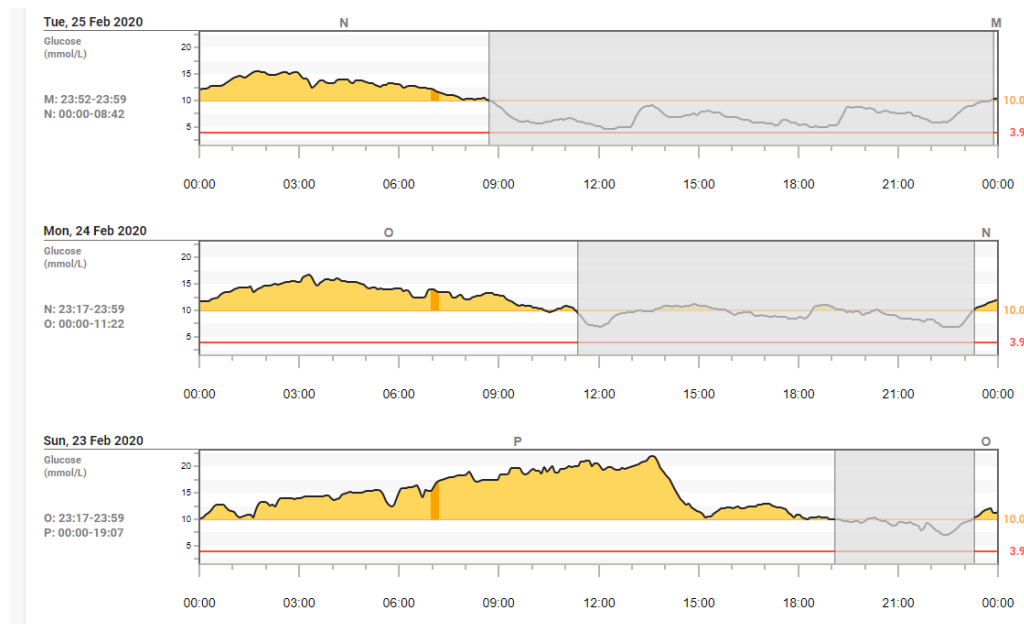
*Background*

Mr. G, a 72-year-old person with T1D for 60 years (diagnosed in 1961), end stage renal disease and coronary artery disease, was treated with basal bolus regimen of insulin since the diagnosis. Following a diagnosis of kidney failure, he was initiated on PD in 2019. He was on APD overnight. Following initiation of PD, his glycaemic control became highly variable with significant high glucose levels >20 mmol/L and low glucose levels <4 mmol/L with impairment of his hypoglycaemia awareness. This persisted despite change in Insulin doses (he was on MDI with BD basal analogue) and frequent home SMBG.

Mr. G was started on CGM (Dexcom G6) in February 2020 with low alert at 5mmol/L.

At the start of the CGM, Mr. G was on insulin detemir twice daily and insulin aspart with meals.

Dexcom clarity data revealed night-time and daytime highs, related to glucose content in PD solutions (Image 1 & 2)



### Image 6.2 – Night-time high glucose pattern recorded in Dexcom while on PD.

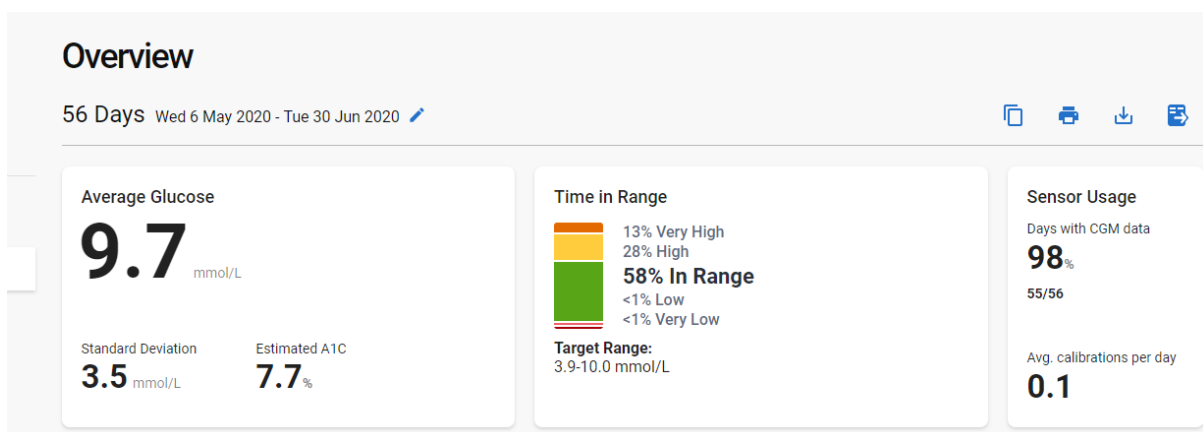
CGM became extremely useful in predicting and increasing awareness on hypoglycaemic episodes, as well as helping to reduce variability by close titration of insulin according to the PD related raised glucose levels.

However, the ability to detect these variable patterns real time made it possible for Mr. G to correct sensibly for these high readings as time went on.

Night-time CGM glucose excursions were noted as expected, while on medium strength glucose containing PD solutions.

His Insulin regime was altered to once a day basal analogue insulin (glargine U300) taken at night.

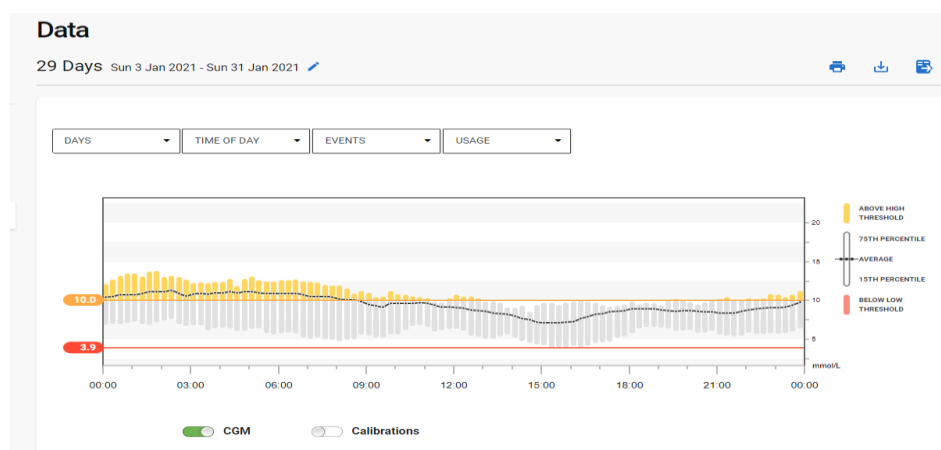
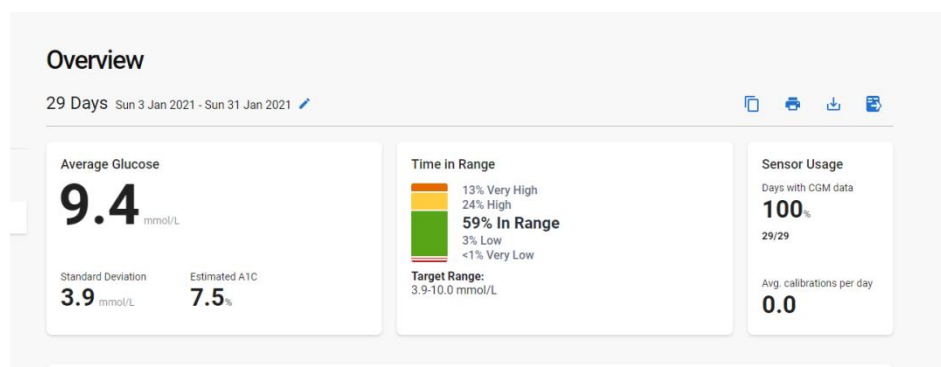
By June 2020, Mr. G demonstrated an overall improvement of his glycaemic control (image 2), contributed by the Dexcom. However, night-time high readings were still persisting.



### Image 6.3 – Overall BG control data of Mr. G from Dexcom clarity by June 2020

Reviewing the data from Dexcom made it possible to titrate insulin according to the changes in dialysate prescription, making it easier for him to control his BG than before.

Currently he is on Insulin glargine U-300 16 Units at night, Fiasp insulin with meals 7-10 Units, Novorapid 5 Units when he starts PD at night with reasonably well BG control than before (Image 3).



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