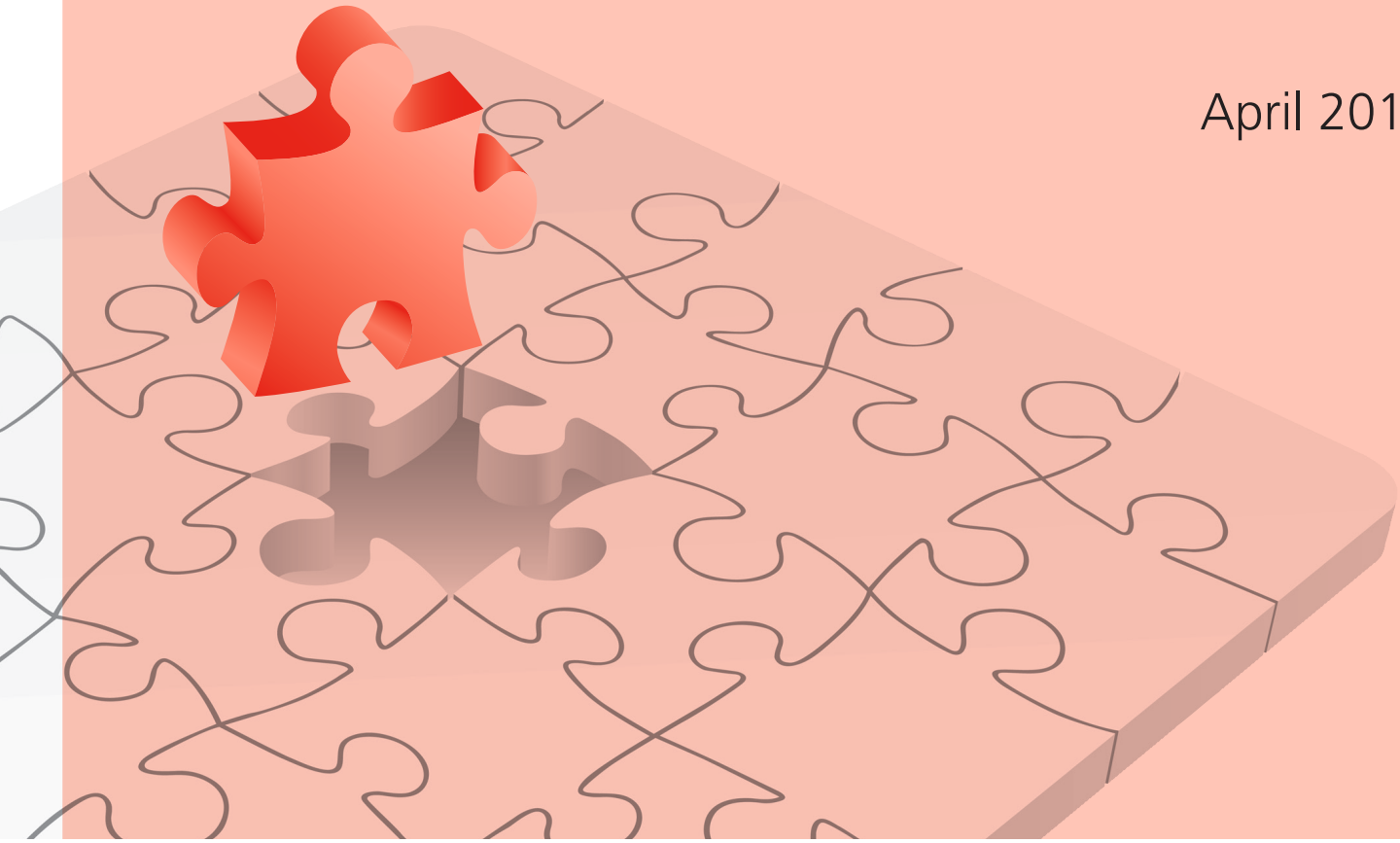
JBDS-IP Joint British Diabetes Societies for inpatient care

Management of adults with diabetes on the haemodialysis unit

April 2016



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and the Diabetes UK website at
www.diabetes.org.uk

Foreword

These guidelines have been commissioned by the Joint British Diabetes Societies in conjunction with the Renal Association. The document has been informed by experts in diabetes and nephrology; including senior clinicians, specialty nurses, dietitians and podiatrists. The aim of these guidelines is to improve the standards of care for people with diabetes who are on maintenance haemodialysis.

The document highlights the organisational difficulties that patients with diabetes on regular hospital haemodialysis experience and the great need for the organisation of their care to be better managed. We hope that these guidelines will be of use to all healthcare professionals whose work brings them in contact with this very vulnerable group of patients.

The target audience specifically includes:

- Clinical staff working on haemodialysis units (nephrologists, haemodialysis specialist nurses and healthcare assistants).
- Clinicians working in diabetes networks (diabetologists, clinical specialist nurses).
- General practitioners practice nurses and district nurses.
- Podiatrists.
- Dietitians involved in the care of patients on haemodialysis.

These are the first national guidelines covering issues relating to diabetes management for this complex group of patients. We hope that they will be a resource which will improve the care, and ultimately the outcomes and quality of life, for this vulnerable patient population.

Methodology

Once the aims and objectives of this guideline were finalised, an outline of its content was produced with specific questions that needed to be addressed in each section. Each section and its corresponding questions were then assigned to an expert in that specific field. A comprehensive literature review was carried out by each one of the contributors for the sections they were responsible for, which provides the evidence base for these recommendations. Where there was little or no evidence, the recommendations are based on expert opinion of the writing team.

Contents

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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

ACCORD	Action to Control Cardiovascular Risk in Diabetes study
BMI	Body mass index
CGM	Continuous glucose monitoring
CKD	Chronic kidney disease
eGFR	Estimated glomerular filtration rate
ESRF	End stage renal failure
GA	Glycated albumin
IDPN	Intra dialysis parenteral nutrition
IDWG	Inter dialysis weight gain
MAGE	Mean amplitude of glucose excursion
MHDx	Maintenance haemodialysis
MODD	Mean of daily differences
ONS	Oral nutritional supplements
PEG	Percutaneous endoscopic gastrostomy
PEW	Protein energy wasting
SMBG	Self monitoring of blood glucose

Summary of all recommendations

Section 1: Organisation of care

1.1. All people with diabetes undergoing maintenance haemodialysis should have a documented annual review of their diabetes which includes foot and eye screening through the GP diabetes register. The responsibility for undertaking this rests with the diabetes service caring for the patient. In order to ensure that this is effectively undertaken:

a. The assessment should be coordinated in a manner that recognises that the patient is dialysing three times per week

b. The information pertaining to the review should be available to all healthcare staff involved in the care of the patient

c. There should be a named link worker on the dialysis unit for each patient who can ensure that the assessments have been undertaken and have been acted upon *(Grade 1B)*

1.2. All people with diabetes undergoing maintenance haemodialysis should have regular 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 work within the diabetes/renal outpatient clinic and provide regular rounds on the dialysis unit, offering patient education and clinical advice where necessary.

A link nurse on the renal 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 to the DSN for specialist foot assessment and ongoing referral to the specialist foot team. *(Grade 1D)*

1.3. A process to coordinate the management of acute metabolic, eye, cardiovascular and/or foot emergencies should be established with effective communication between the dialysis unit, the specialist diabetes team and primary care. *(Grade 1C)*

1.4 All diabetes patients on maintenance haemodialysis programmes with acute and/or chronic glycaemic instability should have specialist diabetes input. *(Grade 1C)*

Section 2: Assessment of glycaemic control

2.1 All units treating patients with diabetes on maintenance haemodialysis should ensure that they are aware of the method used to measure glycated haemoglobin (HbA1c) within their local laboratory and this should ideally be using an HPLC based assay to prevent the overestimation of HbA1c due to carbamylation of haemoglobin. *(Grade 1A)*

2.2 Units managing patients with diabetes on maintenance haemodialysis should be aware of factors that are likely to render HbA1c less reliable including:

- Recent transfusions;
- Haemaglobinopathy;
- Rapid rise of haemoglobin in the preceding 2 months in response to erythropoietin. (Grade 1A)

2.3 Clinicians managing patients with diabetes on maintenance haemodialysis should be aware that it is more likely that the HbA1c will underestimate average blood glucose particularly in patients with good to moderate glycaemic control. *(Grade 1B)*

2.4 Glycated albumin may offer the opportunity to assess glycaemic control over a shorter time period (15–20 days) and with greater accuracy in patients with diabetes on maintenance haemodialysis. This assay is not widely available and has not yet been fully validated such that the use of this assay in assessing glycaemic control in these circumstances should be undertaken as part of a clinical research programme. *(Grade 2C)*

2.5 The use of self monitoring of blood glucose (SMBG) remains a cornerstone of the assessment of glycaemic control in patients with diabetes on maintenance haemodialysis who are being treated with agents that increase the risk of hypoglycaemia. *(Grade 1A)*

2.6 The reliability of SMBG should be augmented by ensuring provision of appropriate equipment, testing strips and training of the operator. *(Grade 1B)*

2.7 Continuous glucose monitoring (CGM) may provide valuable information on the glycaemic control of patients with diabetes on maintenance haemodialysis, however, its use is limited by technical issues relating to device calibration, which must be taken into account for accurate interpretation of data. *(Grade 1C)*

2.8 When using CGM, it is advised to commence the CGM on a non-dialysis day to minimise calibration problems caused by rapid changes in blood glucose due to the dialysis process. *(Grade 1C)*

Section 3: Glycaemic control and outcomes in patients on maintenance haemodialysis

3.1 The target for HbA1c in patients with diabetes and on maintenance haemodialysis should be individualised but if the patient is on a hypoglycaemia inducing treatment should be aimed at between 58–68 mmol/mol (7.5–8.5%). *(Grade 1C)*

3.2 It is likely that HbA1c of >80 mmol/mol (9.5%) represents poor glycaemic control unless there is severe iron deficiency. *(Grade 2C)*

3.3 Reduction in treatment should be considered for patients with HbA1c <58 mmol/mol (7.5%) on treatments associated with increased risk of hypoglycaemia. *(Grade 1C)*

Section 4: Antidiabetic therapies

4.1 Sulfonylureas are not licensed for use in patients on maintenance haemodialysis and should be avoided because of the increased incidence of hypoglycaemia in this setting. *(Grade 1B)*

4.2 Repaglinide can be considered in the haemodialysis patient. Dose reductions are to be expected and it should be noted that experience in this group is limited therefore increased monitoring is required. *(Grade 2C)*

4.3 Metformin is not licensed to be used in patients on maintenance haemodialysis and should be avoided because of the increased risk of lactic acidosis in this setting. *(Grade 1B)*

4.4 Acarbose is not licensed for patients on maintenance haemodialysis. *(Grade 2D)*

4.5 No dose adjustment is needed for pioglitazone for impaired renal function. Whilst pioglitazone is not licensed for use in patients with maintenance haemodialysis there has been some experience of this agent used in this context. *(Grade 1C)*

4.6 There is insufficient experience of the use of any of the current GLP-1 agents in patients on maintenance haemodialysis such that their use cannot be recommended. *(Grade 2D)*

4.7 Of the DPP4 inhibitors licensed in the UK, linagliptin, sitagliptin, vildagliptin and alogliptin can be used in patients on maintenance haemodialysis; however, dose reductions for sitagliptin, vildagliptin and alogliptin are required. *(Grade 1B)*

4.8 SGLT2 inhibitors may be used in patients with early stage chronic kidney disease (CKD; stages 1–2) with no dose adjustment, but as CKD progresses to moderate and severe disease (stages 3–5) they are to be avoided. *(Grade 1C)*

4.9 All people with diabetes on insulin should be dialysed against a dialysate containing glucose. *(Grade 1C)*

4.10 The aim of insulin therapy in diabetes patients on maintenance haemodialysis is to improve quality of life and avoid extremes of hypo- and hyperglycaemia. (Grade 1D)

4.11 Most patients on dialysis would benefit from reduction of insulin doses during and immediately following dialysis (i.e. on the dialysis day), although advice should be individualised ideally on the basis of CGM data. *(Grade 1C)*

4.12 Basal bolus regimes may be most flexible and best suited to the glycaemic variability seen in patients with diabetes on maintenance haemodialysis. *(Grade D, expert opinion)*

4.13 In patients who are less likely to be able to comply with the requirements of a basal bolus regime consideration should be given to once daily regimes with longer acting insulins. *(Grade 1D)*

4.14 CGM may allow clinicians to advise on variation of insulin regimen according to day of dialysis. *(Grade 1D)*

4.15 If patients have troublesome hypoglycaemia on NPH insulin, conversion to analogue insulins may be of benefit. *(Grade 1C)*

Section 5: Dietary management and nutrition

5.1 Each Haemodialysis unit should have access to appropriate dietary expertise able to provide a holistic approach to the patient with diabetes. *(Grade 1D)*

Dietary advice should be personalised and include information on both diabetes and renal aspects of the diet. *(Grade 1D)*

5.2 It is recommended that patients on haemodialysis achieve an energy intake of 30–40 kcal/kg ideal body weight (IBW). *(Grade 1D)*

If a patient is aiming to lose weight appropriate individualised advice should be provided on energy requirements. *(Grade 1D)*

5.3 It is recommended that patients on haemodialysis achieve a protein intake of >1.1 g/kg IBW. *(Grade 1C)*

5.4 Dietary advice should be given for both dialysis and non-dialysis days to minimise significant glycaemic and caloric excursions. *(Grade 1D)*

5.5 The type of diabetes the patient has should be identified and the dietary aims agreed. (Grade 1C)

Total energy should come from 50–60% carbohydrate, <30% fat and at least 15% from protein. *(Grade 1D, expert opinion)*

5.6 Low-potassium fruit, vegetables and carbohydrates with low-moderate glycaemic index should be encouraged to allow patients to achieve the recommended '5-a-day' fruit and vegetable portions. *(Grade 1D)*

5.7 Foods containing phosphate additives should be targeted prior to advice on reducing low GI foods e.g. wholegrain products and foods with high biological protein. *(Grade 1D)*

5.8 A salt intake of <6 g/day is recommended. *(Grade 1C)*

5.9 Oily fish should be recommended with caution for patients with CKD on haemodialysis, mainly because of vitamin A and phosphate content. *(Grade 2D)*

5.10 It is recommended that patients on maintenance haemodialysis are prescribed a water-soluble vitamin supplement. *(Grade 2D)*

5.11 All patients should be screened for protein energy wasting (PEW) on each admission to hospital. If no screening procedures are in place at dialysis units, a referral pathway and/or referral criteria should be in place to identify those at risk for appropriate referral to the dietitian for nutrition support. *(Grade 1D)*

5.12 Initiation of nutrition support should be considered in those at risk of PEW; the indicators are the same in patients with and without diabetes. *(Grade 1C)*

5.13 Dietary counselling and oral nutrition support is the first-line treatment for patients who are unable to meet their nutritional needs orally.

Nasogastric, gastrostomy, or intradialytic parenteral nutrition feeding may be necessary if these interventions are insufficient. *(Grade 1D)*

5.14 The dietary advice and nutritional products prescribed should minimise any deleterious effects on blood sugar or lipid levels. Regular review of the nutritional intervention should be maintained to monitor this. *(Grade 1D)*

5.15 In patients on active treatment of diabetes with insulin:

- Where there is a pre-dialysis glucose of <7 mmol/L, 20–30 g of a low glycaemic index carbohydrate is recommended at the beginning of the haemodialysis session to prevent further decline of blood glucose level. *(Grade 1D)*
- Capillary glucose should be assessed pre- and post-dialysis. *(Grade 1D)*
- The unit should ensure a hypoglycaemia treatment is accessible to patient at all times, including during travelling to and from the dialysis unit. *(Grade 2D)*

5.16 In case of hypoglycaemia:

- Appropriate rapid-acting carbohydrate treatment should be provided to take into account fluid, potassium and phosphate restrictions. *(Grade 1D)*
- 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)*
- Patients and staff should be educated in regard to the appropriate treatment of mild to moderate hypoglycaemia and hypoglycaemia unawareness. *(Grade 1D)*

5.17 Patients with gastroparesis are encouraged to have a small meal size but frequent intake. A low-fat and low-fibre meal is recommended to manage gastroparesis. *(Grade 1C)*

5.18 Clinicians should ensure that patients on maintenance haemodialysis with diabetes are aware that they are more likely to be able to maintain intra-dialytic weight gain (IDWG) at <4.5% of dry weight or <2 kg if they optimise their HbA1c. *(Grade 1C)*

5.19 Overweight/obese patients who are being considered for a kidney transplant should be encouraged to lose weight. Dietary counselling should be a calorie restrictive diet, making sure that the protein requirements for the patient are met (≥1.1 g/kg IBW). *(Grade 1B)*

5.20 Dietary counselling should also ideally include behavioural change strategies and increased physical activity. *(Grade 1B)*

5.21 All patients with an elevated BMI who may not be considered for transplantation if unable to lose weight through diet, exercise and behavioural change should be considered for bariatric surgery or weight-reducing medication. *(Grade 1C)*

Section 6: Complications of diabetes in haemodialysis patients

6.1 In managing patients with diabetes on maintenance haemodialysis, clinicians should be aware of the significantly increased risk of hypoglycaemia caused by

- Poor or erratic nutritional intake;
- Reduced clearance of endogenous or exogenous insulin by the kidney and the liver;
- Decreased hepatic gluconeogenesis. *(Grade 1B)*

6.2 Patients with diabetes on maintenance haemodialysis should be adequately counselled on the increased risk of hypoglycaemia and that hypoglycaemia can occur with diminished classical symptoms. *(Grade 1B)*

6.3 Clinicians should counsel patients with diabetes and on maintenance haemodialysis about risk of hypoglycaemia on dialysis days, and consider reducing anti-hyperglycaemic therapy on dialysis days. (Grade 1D). NB: SEE RECOMMENDATION 5.15: Patients on maintenance haemodialysis on active treatment of diabetes with insulin or oral hypoglycaemic agent(s), should have capillary glucose assessed pre- and post-dialysis.

6.4 The heels of all patients with diabetes on haemodialysis should be protected with a suitable pressure relieving device during haemodialysis. *(Grade 2D)*

6.5 All patients with diabetes on dialysis should have their feet inspected at least weekly. *(Grade 2D)*

6.6 All patients with diabetes on dialysis should be considered high risk and should have regular review by the podiatry team. *(Grade 1C)*

6.7 Patients should have their feet screened three monthly using a locally agreed tool and by competent staff on the dialysis unit. *(Grade 1C)*

6.8 If the patient has an ulcer or there is any other concern the patient should be referred to the diabetic foot multidisciplinary team within one working day. *(Grade 1D)*

6.9 If the patient is on home dialysis it is the responsibility of the clinician in charge of their care (nephrologist or diabetologist) to ensure that the patient has an annual foot review and is attending review by the foot protection team. *(Grade 1D)*

6.10 Any patient presenting with a hot swollen foot should be referred to the diabetic foot team within 24 hours. *(Grade 1D)*

6.11 Patients with diabetes on MHDx approaching end of life or where a palliative care pathway has been agreed should be managed in accordance with Diabetes UK End of Life clinical care recommendations for patients with diabetes. Treatment and interventions should be focussed on symptoms. *(Grade 1D)*

Section 1: Organisation of care

All recommendations

1.1. All people with diabetes undergoing maintenance haemodialysis should have a documented annual review of their diabetes which includes foot and eye screening through the GP diabetes register. The responsibility for undertaking this rests with the diabetes service caring for the patient. In order to ensure that this is effectively undertaken:

a) The assessment should be coordinated in a manner that recognises that the patient is dialysing three times per week

b) The information pertaining to the review should be available to all healthcare staff involved in the care of the patient

c) There should be a named link worker on the dialysis unit for each patient who can ensure that the assessments have been undertaken and have been acted upon *(Grade 1B)*

1.2. All people with diabetes undergoing maintenance haemodialysis should have regular 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 work within the diabetes/renal outpatient clinic and provide regular rounds on the dialysis unit, offering patient education and clinical advice where necessary.

A link nurse on the renal 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 to the DSN for specialist foot assessment and ongoing referral to the specialist foot team. *(Grade 1D)*

1.3. A process to coordinate the management of acute metabolic, eye, cardiovascular and/or foot emergencies should be established with effective communication between the dialysis unit, the specialist diabetes team and primary care. *(Grade 1C)*

1.4 All diabetes patients on maintenance haemodialysis programmes with acute and/or chronic glycaemic instability should have specialist diabetes input. *(Grade 1C)*

1.1 Epidemiology

Chronic kidney disease (CKD) and type 2 diabetes are long term conditions that are recognised as major public health concerns in the UK. The prevalence of CKD has increased in parallel with that of obesity and type 2 diabetes.[1] Moreover, diabetes is currently the leading cause of end-stage renal failure (ESRF) in the developed world accounting for 40% of new ESRF cases in the USA[2] and 25% of incident cases in the UK.[3] The number of adults with type 2 diabetes is increasing and is projected to increase to approximately 642 million in the year 2040.[4] ESRF associated with diabetes is therefore expected to become even more prevalent in the future.

1.2 Association of diabetes with morbidity and mortality in patients on maintenance haemodialysis

Diabetes is a well-recognised risk factor for cardiovascular disease, which is the leading cause of morbidity and mortality in these patients.[5,6] Unfortunately, despite many advances in medicine and renal replacement therapy, the mortality rates for dialysis patients are still high, with 10% first-year mortality rate for patients on maintenance haemodialysis (MHDx) reported in the UK.[3] Patients with diabetes are at a particularly high risk and the overall survival on MHDx in patients with diabetes is about half that of their non-diabetic peers (3.7 vs. 7 years).[3]

A number of areas relating to diabetes care of patients on MHDx remain poorly understood, including targets for glycaemic control and treatment algorithms to achieve them. No national or international guidance was available previously for this group of patients. These guidelines have been produced as a result of collaboration between renal and diabetes specialists. Recommendations have been made based on the best available evidence where it exists and on expert opinion where (more commonly) there is no clear evidence to inform practice. The document aims to provide clear advice to clinicians caring for patients with diabetes on MHDx in relation to a range of issues that cover diabetes care. We also aim to encourage and improve education for both clinicians and patients in order to improve patient empowerment and self-management.

1.3 Organisational requirements of patients with diabetes on maintenance haemodialysis

Recommendation 1.1:

All people with diabetes undergoing maintenance haemodialysis should have a documented annual review of their diabetes which includes foot and eye screening through the GP diabetes register.

The responsibility for undertaking this rests with the diabetes service caring for the patient. In order to ensure that this is effectively undertaken:

a) The assessment should be coordinated in a manner that recognises that the patient is dialysing 3 times per week

b) Information pertaining to the review should be available to all healthcare staff involved in the care of the patient

c) There should be a named link worker on the dialysis unit for each patient who can ensure that the assessments have been undertaken and have been acted upon *(Grade 1B)*

Recommendation 1.2:

All people with diabetes undergoing maintenance haemodialysis should have regular 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 work within the diabetes/renal outpatient clinic and provide regular rounds on the dialysis unit, offering patient education and clinical advice where necessary.

A link nurse on the renal 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 to the DSN for specialist foot assessment and ongoing referral to the specialist foot team. *(Grade 1D)*

Throughout this guidance there will be reference to the need for close surveillance and care of all diabetes patients on MHDx. But – whose responsibility is it to provide this service? General Practitioners (GPs) will remain the key provider of ongoing care, but this patient group have complex medical needs and their daily life is built around the dialysis schedule.[7] As a result, patients may be less likely to attend the GP practice for a routine annual review or diabetes support. Patients with ESRF also come under the remit of specialist diabetes care. Ideally, all patients undergoing MHDx should be reviewed in combined renal diabetes clinics,[8] but, as in general practice, attendance rates are often low and such clinics are not well established. The low participation of patients with diabetes and MHDx is most likely related to the fact that many of these patients are elderly, socially deprived and with a dialysis schedule dominates their life.

Recommendation 1.3:

A process to coordinate the management of acute metabolic, eye, cardiovascular and/or foot emergencies should be established with effective communication between the dialysis unit, the specialist diabetes team and primary care. *(Grade 1C)*

There may also be a misunderstanding of the care provided within haemodialysis units and an assumption that care is being delivered. There may be confusion between renal, diabetes and primary healthcare professionals as to the responsibility for diabetes care, suggesting that many patients on MHDx may not be given routine diabetes care due to multiple appointments or because they feel too ill to attend diabetes clinics.[9]

Recommendation 1.4:

All diabetes patients on maintenance haemodialysis programmes with acute and/or chronic glycaemic instability should have specialist diabetes input. *(Grade 1C)*

Diabetes specialist nurses (DSN) can support, educate and empower such patients and staff.[10] Their review of individuals on dialysis units alongside a dialysis nurse would ensure that all individuals have ongoing diabetes support and that there is timely intervention.

The need for secondary diabetes care is an all important step in providing access to a specialist multi professional team. The provision of a DSN with an interest in diabetes renal care provides this vital link between all specialities. The National Service Framework (NSF) for diabetes,[11] the NSF for renal services[12] and NHS England all emphasise the importance of a multidisciplinary approach in the management of this extremely complex cohort of patients.

National recommendations from Diabetes UK emphasise that care for diabetes patients on MHDx should be undertaken by appropriately trained and competent staff.[13] Primary care, nephrology and diabetes services need to work together to ensure effective communication and care co-ordination: processes, commissioning and contracting agencies therefore need to ensure that these key messages are considered when agreeing new systems for diabetes patients undergoing renal replacement therapy.[14–18]

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Section 2: Assessment of glycaemic control

All recommendations

2.1 All units treating patients with diabetes on maintenance haemodialysis should ensure that they are aware of the method used to measure HbA1c within their local laboratory and this should ideally be using an HPLC based assay to prevent the overestimation of HbA1c due to carbamylation of haemoglobin. (Grade 1A)

2.2 Units managing patients with diabetes on maintenance haemodialysis should be aware of factors that are likely to render HbA1c less reliable including:

- Recent transfusions;
- Haemaglobinopathy;
- Rapid rise of haemoglobin in the preceding 2 months in response to erythropoietin. *(Grade 1A)*

2.3 Clinicians managing patients with diabetes on maintenance haemodialysis should be aware that it is more likely that the HbA1c will underestimate average blood glucose particularly in patients with good to moderate glycaemic control. *(Grade 1B)*

2.4 Glycated albumin may offer the opportunity to assess glycaemic control over a shorter time period (15–20 days) and with greater accuracy in patients with diabetes on maintenance haemodialysis. This assay is not widely available and has not yet been fully validated such that the use of this assay in assessing glycaemic control in these circumstances should be undertaken as part of a clinical research programme. *(Grade 2C)*

2.5 The use of self monitoring of blood glucose (SMBG) remains a cornerstone of the assessment of glycaemic control in patients with diabetes on maintenance haemodialysis who are being treated with agents that increase the risk of hypoglycaemia. *(Grade 1A)*

2.6 The reliability of SMBG should be augmented by ensuring provision of appropriate equipment, testing strips and training of the operator. *(Grade 1B)*

2.7 Continuous glucose monitoring (CGM) may provide valuable information on the glycaemic control of patients with diabetes on maintenance haemodialysis, however, its use is limited by technical issues relating to device calibration, which must be taken into account for accurate interpretation of data. *(Grade 1C)*

2.8 When using CGM, it is advised to commence the CGM on a non-dialysis day to minimise calibration problems caused by rapid changes in blood glucose due to the dialysis process. *(Grade 1C)*

2.1 HbA1c in patients on maintenance haemodialysis

HbA1c, the product of the irreversible non-enzymatic glycation of one or both amino-terminal valine residues of the beta-haemoglobin chain,[1] remains the most widely used tool for assessing patients' glycaemic management. The HbA1c measurement averages blood glucose values over the half-life of the red blood cells (RBC), which is about 50–55 days in the general population.

The relationship between HbA1c and plasma glucose levels was defined in patients with type 1 diabetes using data from the Diabetes Control and Complications Trial (DCCT). The A1c Derived Average Glucose Study Group performed an international multicentre study to examine the relationship over time between average glucose, assessed as completely as possible with a combination of continuous glucose monitoring (CGM) and frequent fingerprick capillary glucose testing, and HbA1c levels. They reported that HbA1c levels can be converted to an estimated average glucose (EAG) level in both type 1 and type 2 diabetes.[2] CKD patients were excluded from this study and therefore the accuracy of this relationship remains unproven in this setting; indeed, there are contradicting reports on the accuracy of the HbA1c values in late CKD stages and haemodialysis, and this should be kept in mind when interpreting these values.[3,4]

Recommendation 2.1:

All units treating patients with diabetes on maintenance haemodialysis should ensure that they are aware of the method used to measure HbA1c within their local laboratory and this should ideally be using an HPLC based assay to prevent the overestimation of HbA1c due to carbamylation of haemoglobin. *(Grade 1A)*

Recommendation 2.2:

Units managing patients with diabetes on maintenance haemodialysis should be aware of factors that are more likely to render HbA1c less reliable including recent transfusions; haemaglobinopathy; rapid rise of haemoglobin in the preceding 2 months in response to erythropoietin. *(Grade 1A)*

Recommendation 2.3:

Clinicians managing patients with diabetes on maintenance haemodialysis should be aware that it is more likely that the HbA1c will underestimate average blood glucose particularly in patients with good to moderate glycaemic control. *(Grade 1B)*

Haemoglobinopathies are known to affect HPLC-based measurements of HbA1c,[5] via at least two mechanisms. One is the presence of an abnormal peak on chromatography, making the estimation of the fraction of HbA1c unreliable. Second, some abnormal forms of haemoglobin (e.g. thalassemia and sickle cell trait) make red blood cells more susceptible to haemolysis. Increased haemolysis corresponds with decreased red cell lifespan, which decreases the time available for glycosylation of haemoglobin chains. These two effects may coexist.

Racial and ethnic differences in the relationship between HbA1c and blood glucose have also been described. Although the reasons for racial and ethnic differences remain unknown, factors such as differences in red cell survival, extracellular-intracellular glucose balance, and nonglycaemic genetic determinants of haemoglobin glycation are being explored as contributors.[6] Twenty-one percent of subjects on renal replacement therapy in the UK were categorised as ethnic minorities, according to the 17th UK Renal Registry Report.[7]

The major factor which contributes to HbA1c inadequacy in renal disease is the altered half-life and turnover of RBCs. Anaemia has been recognised as an important clinical manifestation of progressive renal disease since the 1800s.[8] The degree of anaemia usually increases with the fall of GFR, and tends to plateau by the time patients reach a stage where they require renal replacement therapy.[9] Major causes of anaemia in these patients include:

- **Relative erythropoietin deficiency** leading to inadequate erythrocyte production is the most important cause of anaemia in ESRF. The other factors listed below may add to the severity of anaemia, but are not as instrumental as the decreased production of erythropoietin by the diseased kidneys.
- **Shortened erythrocyte survival:** the lifespan of RBCs reduces from 120 days in normal subjects to 70–80 days in uraemic individuals.[10] This has been attributed to both metabolic causes (decreased activity of sodium and potassium pumps influencing shape and rigidity of RBCs) and mechanical factors (blood loss as explained below).
- **Blood loss** can be due to residual blood left in dialysers, vascular access punctures, occasional blood leaks, phlebotomy for routine testing and clotted dialysers.
- **Iatrogenic haemolysis:** the membranes of the RBCs in patients on dialysis are sensitive to oxidant drugs and chemicals.[11] If tap water is used in the dialysate, the presence of copper, zinc, aluminium, nitrates or chloramine can lead to haemolysis.[12–14]
- **Splenic dysfunction:** a significant number of patients on dialysis have hypersplenism which increases removal of RBCs from the circulation.[15]
- **Mechanical fragmentation:** RBCs can also be injured and deformed by mechanical trauma of the dialysis process and removed from the circulation.[16]
- **Inhibition of erythropoiesis:** it has been suggested that an as yet unidentified factor in uraemic serum may have an inhibitory effect on erythroid precursors.[17]
- **Nutritional factors contributing to anemia:** malnutrition is a common consequence of ESRF and dialysis, and is mainly due to anorexia, intercurrent illness, dialysate nutrient loss and dietary restrictions.[18]

Certain other conditions have long been known to decrease the reliability of HbA1c as they either interfere with the HbA1c assay, or affect RBC survival and in turn cause a 'disproportionate' HbA1c value.

Potential for overestimation of HbA1c in ESRF:

- **An increased level of blood urea nitrogen** can lead to the formation of carbamylated haemoglobin. HbA1c assays that use electrical charge-based methods cannot differentiate between glycated and carbamylated haemoglobin.[19]
- **Uraemia** itself can also lead to an increased glycosylation rate caused by abnormal non-enzymatic glycosylation of proteins in this setting, which is independent of carbamylation reactions and seems to be partially corrected by haemodialysis.[20]
- **Iron deficiency**, common in haemodialysis, leads to increased HbA1c which is reversed by iron replacement therapy.[21]
- **Metabolic acidosis** in uremic patients has been implicated in carbamylation and influences HbA1 levels, but its effect on current estimation of HbA1c is unknown.[22]

Potential for underestimation of HbA1c in ESRF:

- **Shortened erythrocyte lifespan in the uremic setting** causes an increased red blood cell turnover rate and therefore may lead to underestimation of HbA1c.[23]
- ESRD patients are more likely to receive **blood transfusions** which are also a cause of HbA1c underestimation.[24]
- **The widespread use of erythropoeitin in ESRF** patients has an influence on HbA1c as this treatment results in a higher proportion of younger RBCs *(particularly if haemoglobin has increased rapidly)* and may lead to underestimation of HbA1c.[25]

Despite the above, HbA1c is still recommended in current guidelines as the main biomarker for assessing glycaemic control in people with CKD.[26]

2.2 Alternative markers of glycaemic control

Because of concerns surrounding the reliability of HbA1c in subjects with ESRD, fructosamine[27] and glycated albumin (GA) have been proposed as potentially better surrogate markers of glycaemic control in patients with renal anaemia and in receipt of erythropoietin.[25,28] Glycation of these proteins is unaffected by either RBC lifespan or treatment with erythropoietin stimulating agents (ESA).[29]

Recommendation 2.4:

Glycated albumin may offer the opportunity to assess glycaemic control over a shorter time period (15–20 days) and with greater accuracy in patients with diabetes on maintenance haemodialysis. This assay is not widely available and has not yet been fully validated such that the use of this assay in assessing glycaemic control in these circumstances should be undertaken as part of a clinical research programme. *(Grade 2C)*

Fructosamine is a measurement of total glycated serum proteins, with GA accounting for approximately 90%.[30] The concentration of fructosamine is influenced strongly by serum protein concentrations and by low molecular weight substances such as urea or uric acid. GA lacks these limitations, and may therefore be superior to fructosamine as an index of glycaemic control in patients with advanced ESRF.[31]

In studies comparing GA and HbA1c, HbA1c was positively associated with haemoglobin concentrations and negatively associated with erythropoietin dosage, whereas these factors and serum albumin concentration did not significantly impact GA. In best-fit multivariate models, haemodialysis status significantly impacted HbA1c levels, without significant effect on GA. In these studies HbA1c levels were systematically underestimated, so that the quality of glycaemic control was overestimated in patients on haemodialysis, especially at the lower end of the spectrum; GA more accurately reflects recent glycaemic control.[28,32,33]

To prospectively assess the impact of GA on patient survival and hospitalisations, quarterly GA and HbA1c levels were longitudinally measured in 444 MHDx and peritoneal dialysis (PD) dialysis patients.[34] For each 5% increase in GA, the risk of death increased by 14%, whilst HbA1c did not predict survival. Restricting the analysis to the 401 patients on haemodialysis, GA significantly predicted risk of death after adjustment for only age, gender, race, and BMI, whereas HbA1c did not.

2.3 Self-monitoring of blood glucose

Recommendation 2.5:

The use of self monitoring of blood glucose (SMBG) remains a cornerstone of the assessment of glycaemic control in patients with diabetes on maintenance haemodialysis who are being treated with agents that increase the risk of hypoglycaemia. *(Grade 1A)*

Recommendation 2.6:

The reliability of SMBG should be augmented by ensuring provision of appropriate equipment, testing strips and training of the operator. *(Grade 1B)*

In addition to HbA1c, SMBG is especially important in subjects receiving treatments that may cause hypoglycaemia, those who suffer from regular hypoglycaemia and those with hypoglycaemia unawareness.

SMBG results are less reliable if the factors listed below are not taken into account. The accuracy of SMBG may be limited by the accuracy of the blood glucose meter, the timing of measurement in relationship to medication and food, the age of the strips used and the expertise of the person carrying out the test. There are many glucose meters on market and there is a need to ensure that those utilised adhere to latest manufacturing standards (ISO 15197[35]).

In patients on MHDx SMBG results can also be affected by haemolysis, anticoagulation, hyperlipidaemia and metabolic acidosis. Other potentially interfering factors include environmental factors (strips should not be exposed to air, humidity, temperature, altitude), sample volume, the use of generic test strips and reuse of strips. As SMBG accuracy is instrument- and user-dependent, it is important to evaluate each patient's monitoring technique at regular intervals.

2.4 Continuous glucose monitoring

CGM can provide an accurate assessment of glucose control and has been shown to be a reliable indicator of real-time blood glucose concentrations in both the general population, and in people with type 2 diabetes on MHDx.[36,37] Indeed, CGM has the potential to revolutionise the monitoring in people with diabetes.[38] Many studies have shown that using a CGM to guide diabetes treatment significantly improves HbA1c and diabetes control.[39–41]

Recommendation 2.7:

Continuous glucose monitoring (CGM) may provide valuable information on the glycaemic control of patients with diabetes on maintenance haemodialysis, however, its use is limited by technical issues relating to device calibration, which must be taken into account for accurate interpretation of data. *(Grade 1C)*

Recommendation 2.8:

When using CGM, it is advised to commence the CGM on a non-dialysis day to minimise calibration problems caused by rapid changes in blood glucose due to the dialysis process. *(Grade 1C)*

Patients can wear CGM devices without restricting their physical mobility or daily routine. This technology generally measures interstitial glucose every few minutes, recording the results in their internal memory, or transmitting them wirelessly to another device, such as a mobile phone, computer or an insulin pump.

CGM is ideally suited for people with diabetes on MHDx. Unlike HbA1c, CGM can reveal short-term glycaemic changes around the time of dialysis, with results that are unaffected by urea, RBC lifespan and RBC production. There are, however, certain limitations for CGM use in haemodialysis subjects. The main area of difficulty when using CGM in MHDx patients relates to the initial calibration process. Most manufacturers depend on a few SMBG readings within a certain timeframe to calibrate the CGM readings. Some devices employ 'retrospective calibration', which means once the monitoring period is completed, SMBG results for certain points of time are entered into the software and the glucose chart produced by the software is adjusted for the patient. The drawback for this type of calibration is that while it is easy and practical, the actual glucose values and the area under the glucose curve derived by this method are very much dependent on the accuracy of the SMBG result (see above). Comparing CGM data between individuals raises further issues; was the same meter used for calibration, was the reading obtained in a reliable fashion, etc. Other devices use 'real-time calibration', where SMBG results are required within a certain timeframe at the beginning of the monitoring session so that the device can be calibrated and start data collection immediately.

Although the real-time calibration method seems to be more accurate, it is actually more problematic in MHDx patients because of the longer time lag between capillary blood glucose (SMBG) and interstitial blood glucose (CGM) for patients with ESRF, which introduces errors and prevents an accurate monitoring period. This issue can be especially problematic if the CGM monitoring period is initiated while the patient is being dialysed and is experiencing a rapid change in blood glucose concentrations which take even longer to show in interstitial fluid glucose concentration measurements. Because CGM measures the glucose in the interstitial fluid, near-hypoglycaemic levels are harder to detect, as the glucose level in the interstitial fluid is maintained for as long as possible and the lag time mentioned above is further increased in ESRF.

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Section 3: Glycaemic control and outcomes in patients on maintenance haemodialysis

All recommendations

3.1 The target for HbA1c in patients with diabetes and on maintenance haemodialysis should be individualised but if the patient is on a hypoglycaemia inducing treatment should be aimed at between 58–68 mmol/mol (7.5–8.5%). *(Grade 1C)*

3.2 It is likely that HbA1c of >80 mmol/mol (9.5%) represents poor glycaemic control unless there is severe iron deficiency. *(Grade 2C)*

3.3 Reduction in treatment should be considered for patients with HbA1c< 58 mmol/mol (7.5%) on treatments associated with increased risk of hypoglycaemia. *(Grade 1C)*

The long-term outcomes benefits from early, intensive intervention to lower glycaemia and HbA1c in patients with type 1 or type 2 diabetes were confirmed by follow-up of the patient populations from the Diabetes Control and Complications Trial (DCCT),[1] and the UK Prospective diabetes study (UKPDS),[2] respectively. It is important later in the course of diabetes to achieve as low a level of glycaemia as possible without inducing hypoglycaemia.[3] Aiming to achieve HbA1c values close to that of the general population (<48 mmol/mol [6.5%]) has been associated with *increased* mortality and no benefit in terms of CVD risk reduction[4]; even the long-established target of <53 mmol/mol (7.0%) in the diabetic population may be harmful in those with long standing type 2 diabetes[5] and trials that claim to show improved survival with lower HbA1c levels only demonstrate marginal survival benefits.[6,7] The CKD subgroup study of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial has shown that subjects with CKD receiving intensive glycaemic management were at greater risk for both cardiovascular and all-cause mortality compared with their non-CKD counterparts.[8] As there are no specific glycaemic management guidelines for patients with ESRF, the same has been assumed to apply to this population.

A 7-year observational study showed that better glycaemic control predicted better survival among patients with diabetes on MHDx,[9] with a further study reaching the same conclusion.[10] However, one should note that the cut-off value for defining good glycaemic control was an HbA1c level of <58 mmol/mol (7.5%), which is higher than conventional HbA1c cut-off values.

A one-year follow-up study of 23,000 American subjects with diabetes suggested that low HbA1c levels may not confer survival benefit in ESRF.[11] However, the apparently counterintuitive association between poor glycaemic control and greater survival may be explained confounding from factors such as malnutrition and anaemia.[12] Overall, higher HbA1c was associated with increased mortality risk and lower HbA1c levels not related to malnutrition or anaemia appeared to be associated with improved survival in patients on MHDx.

A study in 9,201 haemodialysis patients with type 1 or type 2 diabetes from 12 countries showed that mortality was lowest at HbA1c 53–63 mmol/mol (7.0–7.9%) and increased progressively for either lower or higher HbA1c levels.[13] The relationship between low HbA1c and mortality appeared to be even stronger in patients with indicators of poor nutritional status, including low serum albumin, low BMI, or the presence of cachexia. These findings suggest that optimal HbA1c levels among haemodialysis patients with diabetes may need to be less stringent than levels recommended for patients with diabetes who do not have CKD.

The DOPPS study highlighted inappropriate prescription of diabetes medicines.[13] These agents were frequently prescribed to haemodialysis patients with HbA1c <42 mmol/mol (6%) and also frequently not prescribed to those with HbA1c ≥75 mmol/mol (9%), which was identified as a readily modifiable practice that may improve clinical outcomes.

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Section 4: Antidiabetic therapies

All recommendations

4.1 Sulfonylureas are not licensed for use in patients on maintenance haemodialysis and should be avoided because of the increased incidence of hypoglycaemia in this setting. *(Grade 1B)*

4.2 Repaglinide can be considered in the haemodialysis patient. Dose reductions are to be expected and it should be noted that experience in this group is limited therefore increased monitoring required. *(Grade 2C)*

4.3 Metformin is not licensed to be used in patients on maintenance haemodialysis and should be avoided because of the increased risk of lactic acidosis in this setting. *(Grade 1B)*

4.4 Acarbose is not licensed for patients on maintenance haemodialysis. *(Grade 2D)*

4.5 No dose adjustment is needed for pioglitazone for impaired renal function. Whilst pioglitazone is not licensed for use in patients with maintenance haemodialysis there has been some experience of this agent used in this context. *(Grade 1C)*

4.6 There is insufficient experience of the use of any of the current GLP-1 agents in patients on maintenance haemodialysis such that their use cannot be recommended. *(Grade 2D)*

4.7 Of the DPP4 inhibitors licensed in the UK, linagliptin, sitagliptin, vildagliptin and alogliptin can be used in patients on maintenance haemodialysis; however, dose reductions for sitagliptin, vildagliptin and alogliptin are required. *(Grade 1B)*

4.8 SGLT2 inhibitors may be used in patients with early stage chronic kidney disease (CKD; stages 1–2) with no dose adjustment, but as CKD progresses to moderate and severe disease (stages 3–5) they are to be avoided. *(Grade 1C)*

4.9 All people with diabetes on insulin should be dialysed against a dialysate containing glucose. *(Grade 1C)*

4.10 The aim of insulin therapy in diabetes patients on maintenance haemodialysis is to improve quality of life and avoid extremes of hypo- and hyperglycaemia. *(Grade 1D)*

4.11 Most patients on dialysis would benefit from reduction of insulin doses during and immediately following dialysis (i.e. on the dialysis day), although advice should be individualised ideally on the basis of CGM data. *(Grade 1C)*

4.12 Basal bolus regimes may be most flexible and best suited to the glycaemic variability seen in patients with diabetes on maintenance haemodialysis. *(Grade D, expert opinion)*

4.13 In patients who are less likely to be able to comply with the requirements of a basal bolus regime consideration should be given to once daily regimes with longer acting insulins. *(Grade 1D)*

4.14 CGM may allow clinicians to advise on variation of insulin regimen according to day of dialysis. *(Grade 1D)*

4.15 If patients have troublesome hypoglycaemia on NPH insulin, conversion to analogue insulins may be of benefit. *(Grade 1C)*

4.1 Non-insulin treatments in patients with end stage renal failure

4.1.1 Principles of glycaemic management in patients with diabetes on maintenance haemodialysis

Declining renal function is known to have diametric opposite effects on glucose metabolism. While peripheral insulin resistance increases, renal gluconeogenesis and hypoglycaemic counter-regulation decrease. The clearance of insulin (endogenous and exogenous) and other antihyperglycaemic agents also declines.

A so-called "burnt-out diabetes" phenomenon has been described, whereby patients with type 2 diabetes on MHDx 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.[1] However, treatment is still required for many of these patients (see Section 6.1).

While insulin therapy is the only therapeutic option in type 1 diabetes, pharmacologic and non-pharmacological treatment options are relevant to the management of type 2 diabetes. This summary will focus on the pharmacological groups used in the treatment type 2 diabetes in haemodialysis patients. It does not discuss treatment algorithms for treatment of diabetes mellitus in haemodialysis patients, which should be individualised based on the safety profile and treatments available locally.

In principle there are nine classes of antihyperglycaemic drugs available for treatment of diabetes mellitus. Not all classes are suitable for use in haemodialysis patients: 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.

4.1.2 Insulin secretagogues, metformin, α-glucosidase inhibitors, thiazolidinediones

Recommendation 4.1:

SU are not licensed for use in patients on maintenance haemodialysis and should be avoided because of the increased incidence of hypoglycaemia in this setting. *(Grade 1B)*

Sulfonylureas (SU) work by closing ATP-sensitive potassium channels on β-cells, which triggers insulin release. They also improve insulin sensitivity through stimulation of transmembrane glucose receptors in muscle and fat cells. Tolbutamide and chlorpropamide are first-generation SU; these were followed by second-generation agents, including glibenclamide, gliclazide and glipizide, and then glimepiride, a third-generation SU.

SU should be used in caution with subjects with G6PD deficiency and should not be used in insulin-dependent diabetes, diabetic coma, ketoacidosis, lactation or pregnancy. Key side-effects of SU are increased body weight (by about 1.5–2.5 kg as monotherapy) and hypoglycaemia.[2] Concerns over possible adverse effects of SU on the cardiovascular system remain a matter for debate.[3]

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 patients to risk of hypoglycaemia. It should be noted that SU are generally highly protein bound and therefore unlikely to be dialysed, which can cause post-dialysis hypoglycaemia. These drugs do not have clear 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).

- **Glibenclamide** is metabolised by the liver and eliminated equally in bile and urine. Some of its metabolites are active and may accumulate in CKD although hepatobiliary elimination may partially compensate for the decrease in renal elimination. Glibenclamide is contraindicated in CKD stages ≥3 (eGFR<60 mL/min).[4,5]
- **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 glibenclamide and glimepiride, should be used with caution when GFR is <40 mL/min.[6]
- **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.[7]
- The metabolism of **glipizide** occurs mainly in 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).[8]

Therefore, the use of SU in patients with type 2 diabetes on MHDx is off-licence.

Recommendation 4.2:

Repaglinide can be considered in the haemodialysis patient. Dose reductions are to be expected and it should be noted that experience in this group is limited therefore increased monitoring required. *(Grade 2C)*

Glinides exhibit insulinotropic effects by stimulating pancreatic SU receptors. Receptor activation is more rapid and shorter than for SU.

- *Repaglinide* is a benzoic acid derivative, whereas *nateglinide* is a phenylalanine derivative.
- Both agents are metabolised in the liver, but while repaglinide is eliminated via the faeces, 80% of nateglinide is excreted renally.[9]
- Repaglinide may be given in all stages of renal failure. After a 5 day treatment of repaglinide (2 mg TID) in patients with severely impaired renal function (creatinine clearance: 20–39 mL/min), there was a significant 2-fold increase of the exposure (AUC) and half-life (t1/2) compared with patients with normal renal function. Dose adjustments should be considered at CKD stages 4–5.[10]
- Both agents have been trialled on small scales in the dialysis populations at lower doses and although they are not licensed for use in patients on haemodialysis they are not contraindicated outright. Both agents are highly protein bound and therefore unlikely to be removed during dialysis.

Recommendation 4.3:

Metformin is not licensed to be used in patients on maintenance haemodialysis and should be avoided because of the increased risk of lactic acidosis in this setting. *(Grade 1B)*

Metformin has no clinical value in the haemodialysis population due to risk of severe lactic acidosis as accumulation occurs in renal failure. It is however mentioned in the document for completion and its potential value in CKD stages 1–3b as highlighted in the UKPDS. The NICE guideline CG87 highlights its prescribing limitations in the context of renal function and provides details of when doses should be reduced (estimated glomerular filtration rate [eGFR] <45 mL/min) or then stopped (eGFR <30 mL/min).[11,12]

Recommendation 4.4:

Acarbose is not licensed for maintenance haemodialysis. *(Grade 2D)*

Acarbose is a pseudo-tetrasaccharide α-glucosidase inhibitor derived from the bacterium, Actinoplanes that 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 has multiple gastrointestinal side-effects.[13]

- Acarbose can be given in CKD stage 1–3 without dose adjustments.
- As acarbose has not been studied in patients with severe renal impairment, it should not be used in patients with a creatinine clearance of less than 25 mL/min/1.73m^2. Therefore, it is not recommended for use in dialysis.

Recommendation 4.5:

No dose adjustment is needed for pioglitazone for impaired renal function. Whilst pioglitazone is not licensed for use in patients with maintenance haemodialysis there has been some experience of this agent used in this context. *(Grade 1C)*

Pioglitazone is the only remaining thiazolidinedione (TZD) on the market (rosiglitazone was withdrawn in 2010 due to significant cardiovascular and osteoskeletal complications) and can be used as monotherapy if metformin is contraindicated.

- The risk of hypoglycaemia is low with pioglitazone and its hepatic metabolism that abolishes the need for dose adjustment when renal function declines.[14]
- It has no renal elimination and is unaffected by haemodialysis15 and can be used in CKD stage 1–5 down to a clearance of 4 mL/min; however. it is not licensed for use if the patient commences on renal replacement therapy.

- The published experience of the use of TZDs in MHDx patients is inconsistent with data suggesting that rosiglitazone use was associated with increased cardiovascular risk.[16] However, a larger study that compared MHDx patients exposed to TZD compared to no exposure was associated with significantly lower all-cause mortality among insulin-free but not insulin-requiring subjects, with adjusted hazard ratios (95%CI) of 0.53 (0.31–0.89) and 0.82 (0.46–1.47), respectively.[17]
- It should be noted that the increased incidence in "heart failure" associated with a TZD is generally caused by salt and water retention. The risk of this in patients on maintenance haemodialysis has not been studied.

4.1.3 Incretin-based therapies

4.1.3.1 Overview

In the mid-1960s, experiments on the differences in insulin release after oral vs. intravenous glucose administration led to the hypothesis that there were unknown glucoregulatory intestinal hormones, now known as incretins. In 1985 glucagon-like peptide (GLP1) was identified but found to be rapidly inactivated by the enzyme, dipeptylpeptidase-4 (DPP4).

Two classes of incretin-based therapy have been developed to overcome this limitation and have been available since 2005–2006:

- **GLP-1 agonists** (currently exenatide [BID and QW formulations], liraglutide [QD], lixisenatide [QD], and dulaglutide [QW]) have limited structural similarities to GLP-1, with increased resistance to DPP4 and prolonged serum half-life relative to native GLP-1.
- **DPP4 inhibitors** (currently sitagliptin [QD], vildagliptin [BID, but QD in the setting of ESRF], saxagliptin [QD], linagliptin [QD], alogliptin [QD]) inhibit the degradation of endogenous GLP-1 and enhance its effects on insulin secretion and glycaemia.

Incretin-based therapies enhance glucose-dependent postprandial insulin secretion and lower pre- and postprandial glycaemia and are indicated for use in patients with type 2 diabetes.

4.1.3.2 GLP-1 receptor agonists

Recommendation 4.6:

There is insufficient experience of the use of any of the current GLP-1 agents in patients on maintenance haemodialysis such that their use cannot be recommended. *(Grade 2D)*

No dose adjustment is necessary for **exenatide** patients with mild renal impairment (creatinine clearance 50–80 mL/min), but clinical experience with exenatide in patients with moderate renal impairment (creatinine clearance 30–50 mL/min) is very limited. Population pharmacokinetic analysis in CKD patients suggest an increase in systemic exposure of approximately 74% (moderate CKD) and 23% (mild CKD), compared with subjects with normal renal function patients.[18]

Liraglutide is a long-acting GLP-1 agonist. No dose adjustment is required for patients with mild or moderate renal impairment (creatinine clearance 60–90 mL/min and 30–59 mL/min, respectively). There is no therapeutic experience with liraglutide patients with severe renal impairment (creatinine clearance <30 mL/min). No specific organ has been identified for the elimination of liraglutide, and caution is recommended for use in patients with severe renal impairment including those with ESRF.[19]

Lixisenatide is available as prefilled pens for subcutaneous injection at lower monthly cost (£54.14 at 20 µg/day at time of writing) compared with exenatide (£68.24) or liraglutide (£78.48). In trials lasting 24 weeks, adjunctive lixisenatide reduced HbA1c by 0.36–0.75% and at least doubled the proportion of patients achieving glycaemic control (HbA1c <7.0%) vs. placebo. Another 24-week study showed lixisenatide to be non-inferior to twice-daily exenatide in reducing HbA1c. Lixisenatide may be preferred to twice-daily exenatide being non-inferior, having better tolerability and only requiring one daily injection. It is eliminated renally, but no dose adjustment is needed until creatinine clearance declines to 50 mL/min. There is limited experience for use in more severe renal dysfunction, such that it cannot be recommended in ESRF/ haemodialysis.[20]

Dulaglutide is a once-weekly GLP-1 receptor agonist. The recommended initiating dose is 0.75 mg once weekly and may be increased to 1.5 mg QW (its maximum recommended dose) for additional glycaemic control.[21] There is limited clinical experience in patients with severe renal impairment or ESRF. Dulaglutide should be used with caution, and if these patients experience adverse gastrointestinal side effects, renal function should be closely monitored.

Post-marketing reports of acute renal failure and worsening of chronic renal failure, which may sometimes require haemodialysis, have appeared for patients treated with GLP-1 receptor agonists. Some of these events were reported in patients without known underlying renal disease. A majority of reported events occurred in patients who had experienced nausea, vomiting, diarrhoea, or dehydration. Because these reactions may worsen renal function, use caution when initiating or escalating doses of GLP-1 receptor agonists in patients with renal impairment and monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions.[22]

4.1.3.3 DPP-4 inhibitors

Recommendation 4.7:

Of the DPP4 inhibitors licensed in the UK, linagliptin, sitagliptin, vildagliptin and alogliptin can be used in patients on maintenance haemodialysis; however, dose reductions for sitagliptin, vildagliptin and alogliptin are required. *(Grade 1B)*

DPP4 inhibitors are not associated with hypoglycaemia and are one of the few therapies with clear recommendations for use in haemodialysis. This has opened up a new range of therapies for dialysis patients, which previously did not exist.

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 dialysis, but is removed by high flux dialysis (13.5 % of the drug is removed by a 3–4 hour dialysis session).[23]

When considering the use of sitagliptin in combination with other antidiabetic medicinal product, its conditions for use in patients with renal impairment should be checked. Dose adjustments for CKD are:

- Mild renal impairment (creatinine clearance ≥50 mL//min) – no dose adjustment.
- Moderate renal impairment (creatinine clearance 30–50 mL/min) – use sitagliptin 50 mg QD.
- Severe renal impairment (creatinine clearance <30 mL/min or ESRF requiring haemodialysis or peritoneal dialysis) – use sitagliptin 25 mg QD.
- Treatment may be administered without regard to the timing of dialysis.[24]

Linagliptin has minimal metabolism to inactive metabolites and approximately 80% is eliminated in the faeces and 5% in the urine.[25] 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 type 2 diabetes patients with severe renal failure was increased by about 1.4-fold compared with type 2 diabetes patients with normal renal function. Steady-state predictions for AUC of linagliptin in patients with ESRF indicated comparable exposure to that of patients with moderate or severe renal impairment. No dose adjustment is required and linagliptin 5 mg QD is suitable for patients on MHDx.[26]

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 AUC increased on average by 1.4-fold, 1.7-fold and 2-fold in patients with mild, moderate and severe renal impairment, respectively, 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.[27]

Vildagliptin is also not removed by conventional dialysis but is by high flux. Three percent of vildagliptin is removed after a 3–4 hour haemodialysis session. The main metabolite (LAY 151) is also removed by haemodialysis.[28] No dose adjustment is required in patients with mild renal impairment (creatinine clearance ≥ 50 mL/min). In patients with moderate or severe renal impairment or with ESRF, the recommended dose is 50 mg QD.[29]

Saxagliptin is used at 2.5 mg or 5mg QD, regardless of meals. Saxagliptin 2.5 mg was compared with placebo in a 52-week trial in 170 type 2 diabetes patients with moderate-to-severe CKD or ESRF; the incidence of adverse events was similar between the two groups.[30] Saxagliptin is eliminated by both renal and hepatic pathways.

- There is no need for dose adjustment of saxagliptin in mild-to-moderate renal impairment
- 2.5 mg once daily is the recommended dose in severe CKD and ESRF.
- Saxagliptin is removed by haemodialysis.[31]

Alogliptin is available as 6.25 mg, 12.5 mg and 25 mg tablets. The efficacy and safety of the recommended doses of alogliptin were investigated separately in a subgroup of patients with type 2 diabetes mellitus and severe CKD/ESRF in a placebo-controlled study (59 patients on alogliptin and 56 patients on placebo for 6 months) and found to be consistent with the profile obtained in patients with normal renal function. Dose adjustments for impaired renal function are:

- Mild renal impairment (creatinine clearance 50–80 mL/min) – no dose adjustment is necessary
- Moderate renal impairment (creatinine clearance 30–50 mL/min) – use alogliptin 12.5 mg QD.[32]
- Severe renal impairment (creatinine clearance < 30 mL/min) or ESRF requiring dialysis – one-quarter of the recommended maximum dose of alogliptin should be administered (6.25 mg QD).

Alogliptin 6.25 mg QD was effective and generally well-tolerated in a 48-week study in 30 patients with type 2 diabetes undergoing haemodialysis.[33] Alogliptin may be administered without regard to the timing of dialysis. Experience in patients requiring renal dialysis is limited.

4.1.4 SGLT2 inhibitors

Recommendation 4.8:

SGLT2 inhibitors may be used in patients with early stage chronic kidney disease (CKD; stages 1–2) with no dose adjustment, but as CKD progresses to moderate and severe disease (stages 3–5) they are to be avoided. *(Grade 1C)*

Sodium-glucose co-transporter-2 (SGLT2) inhibitors are a new group of oral medications used for treating type 2 diabetes. They inhibit glucose reabsorption in the proximal renal tubules 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 some antihypertensive qualities due to simultaneous urinary excretion of sodium. Three SGLT2 inhibitors are currently available for prescription: dapagliflozin, canagliflozin and empagliflozin.

The glucose-lowering efficacy and safety of SGLT2 inhibitors are almost comparable in patients with mild CKD (eGFR >50 mL/min) and patients with normal kidney function. These agents have also been shown to be effective on glycaemia and generally well tolerated in subjects with type 2 diabetes and Stage 3 CKD.[34] Their efficacy tends to be reduced and safety concerns may occur in patients with moderate CKD, and the use of SGLT2 inhibitors is contraindicated in severe CKD.[35]

4.2 Insulin in patients with end stage renal failure

4.2.1 Glycaemic regulation and haemodialysis

Recommendation 4.9:

All people with diabetes on insulin should be dialysed against a dialysate containing glucose. *(Grade 1C)*

Renal impairment leads to a net reduction in insulin requirement as increases in insulin resistance and reduced insulin secretion are offset by reduced renal insulin clearance. Reductions in total insulin requirements parallel reductions in eGFR, with a reduction in insulin requirement of about 50% when eGFR falls to <10 mL/min.[36]

Pharmacological management of diabetes for people with ESRF is limited by the reduced number of therapeutic options. Frequently, insulin is the only available therapeutic option, and whilst careful management of glycaemia with insulin is feasible, patients are at particular risk of hypoglycaemia and glycaemic variability.

The process of haemodialysis has a number of effects on glycaemic control:

- Haemodialysis effectively clears a number of glucoregulatory hormones, including insulin, C-peptide and glucagon.[37]
- Haemodialysis may affect insulin secretion, clearance, and resistance as the result of periodic improvement in uraemia, acidosis, and phosphate metabolism.
- Glucose concentration in the dialysate may also influence glucose control, with lower glucose dialysates being associated with hypoglycemia.[38]
- Dialysis may affect the clearance of antidiabetic therapy such as insulin or SU.

Furthermore, blood glucose tends to fall during a haemodialysis session, with the nadir during the third hour, including in non-diabetic patients, although hypoglycaemic episodes are not common in this population.[39,40] Therefore, glucose control on dialysis days may be very different to that on non-dialysis days, leading to unpredictable glucose levels, and glycaemic variability.

A so-called "burnt-out diabetes" phenomenon has been described, whereby patients with type 2 diabetes on MHDx experience frequent hypoglycaemic episodes leading to cessation of their antidiabetic therapies transiently or permanently.[41] Most patients with diabetes on MHDx will require some therapy for hyperglycaemia, however. This is complicated by significantly lower mean glucose concentrations in subjects with diabetes on dialysis days compared with non-dialysis days.[42] One study using 24-hour CGM found that 75% of hypoglycaemic events and 82% of nadir glucose levels occurred within 24 hours of dialysis.[43] A further study suggested that glycaemic variability was greatest on the dialysis days compared to non-dialysis days.[44] This suggests that variation of oral hypoglycaemic or insulin therapy may be required on day of dialysis.

4.2.2 Insulin regimen options in patients with diabetes on MHDx

Recommendation 4.10:

The aim of insulin therapy in diabetes patients on maintenance haemodialysis is to improve quality of life and avoid extremes of hypo- and hyperglycaemia. *(Grade 1D)*

Recommendation 4.11:

Most patients on dialysis would benefit from reduction of insulin doses during and immediately following dialysis (i.e. on the dialysis day), although advice should be individualised ideally on the basis of CGM data. *(Grade 1C)*

Recommendation 4.12:

Basal bolus regimes may be most flexible and best suited to the glycaemic variability seen in patients with diabetes on maintenance haemodialysis. *(Grade D, expert opinion)*

Recommendation 4.13:

In patients who are less likely to be able to comply with the requirements of a basal bolus regime consideration should be given to once daily regimes with longer acting insulins. *(Grade 1D)*

Recommendation 4.14:

CGM may allow clinicians to advise on variation of insulin regimen according to day of dialysis. *(Grade 1D)*

Recommendation 4.15:

If patients have troublesome hypoglycaemia on NPH insulin, conversion to analogue insulins may be of benefit. *(Grade 1C)*

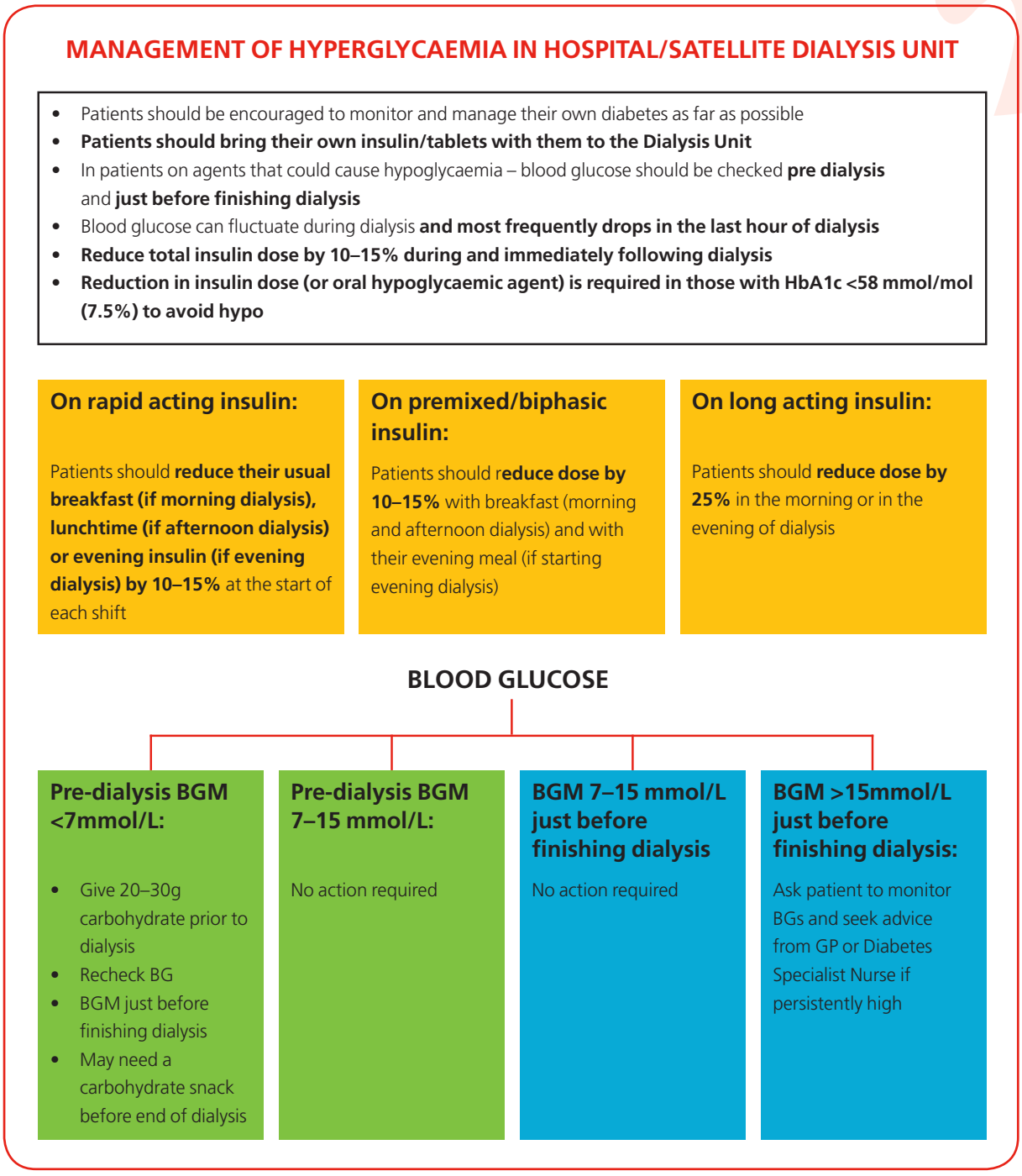
The aim of glycaemic therapy in patients on MHDx should be to enhance quality of life, and to reduce extremes of glycaemia. Evidence from observational studies suggests a "U" shaped curve of glycaemic control in patients on MHDx, with one study suggesting a lowest mortality seen at HbA1c 53–63 mmol/mol (7.0–7.9%).[45]

Basal-bolus insulin with regular capillary glucose monitoring may be the safest regimen, given the increased sensitivity to insulin associated with haemodialysis and the risk of hypoglycaemia (see Fig. 1). A study using 24-hour euglycaemic clamp methodology in patients with type 2 diabetes on MHDx demonstrated a 25% reduction in basal insulin requirements immediately following a haemodialysis session.[45] Therefore, a reduction of basal insulin dose on the day of dialysis seems a reasonable precaution to avoid hypoglycaemia.

One small study suggests that using basal insulin glargine may reduce hypoglycaemia compared with NPH insulin in patients on MHDx.[46] Two other small studies suggested that thrice-weekly long-acting insulin injections at the end of dialysis improved glycaemic control significantly in diabetes patients on MHDx.[47,48]

Biphasic insulin regimens may be more difficult to manage on haemodialysis due to the irregularity of diet, glucose levels and activity imposed by haemodialysis sessions. Nevertheless, many people on MHDx with long standing diabetes may have been on biphasic insulin regimes for some years, and be reluctant to progress to basal bolus regimes. Therefore, advice on 10–15% reduction in doses of insulin on dialysis days may be required to avoid hypoglycaemia (Fig. 1).

Fig. 1. Managing insulin regimens on people with diabetes on maintenance haemodialysis.



4.2.3 Research Recommendation

A trial of longer acting insulin (e.g. degludec) given after dialysis 3 times/week should be conducted for patents who require district nurses, have difficulty going on to insulin, or have difficulty injecting insulin.

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Section 5: Dietary recommendations

All recommendations

5.1 Each Haemodialysis unit should have access to appropriate dietary expertise able to provide a holistic approach to the patient with diabetes. *(Grade 1D)*

Dietary advice should be personalised and include information on both diabetes and renal aspects of the diet. *(Grade 1D)*

5.2 It is recommended that patients on haemodialysis achieve an energy intake of 30–40 kcal/kg ideal body weight (IBW). *(Grade 1D)*

If a patient is aiming to lose weight appropriate individualised advice should be provided on energy requirements. *(Grade 1D)*

5.3 It is recommended that patients on haemodialysis achieve a protein intake of >1.1 g/kg IBW *(Grade 1C)*

5.4 Dietary advice should be given for both dialysis and non-dialysis days to minimise significant glycaemic and caloric excursions. *(Grade 1D)*

5.5 The type of diabetes the patient has should be identified and the dietary aims agreed. *(Grade 1C)*

Total energy should come from 50–60% carbohydrate, <30% fat and at least 15% from protein. *(Grade 1D, expert opinion)*

5.6 Low-potassium fruit, vegetables and carbohydrates with low-moderate glycaemic index should be encouraged to allow patients to achieve the recommended '5-a-day' fruit and vegetable portions. *(Grade 1D)*

5.7 Foods containing phosphate additives should be targeted prior to advice on reducing low glycaemic index foods e.g. wholegrain products and foods with high biological protein. *(Grade 1D)*

5.8 A salt intake of <6 g/day is recommended. *(Grade 1C)*

5.9 Oily fish should be recommended with caution for patients on haemodialysis, mainly because of vitamin A and phosphate content. *(Grade 2D)*

5.10 It is recommended that patients on maintenance haemodialysis are prescribed a water-soluble vitamin supplement. *(Grade 2D)*

5.11 All patients should be screened for protein energy wasting (PEW) on each admission to hospital. If no screening procedures are in place at dialysis units, a referral pathway and/or referral criteria should be in place to identify those at risk for appropriate referral to the dietitian for nutrition support. *(Grade 1D)*.

5.12 Initiation of nutrition support should be considered in those at risk of PEW; the indicators are the same in patients with and without diabetes. *(Grade 1C)*

5.13 Dietary counselling and oral nutrition support is the first-line treatment for patients who are unable to meet their nutritional needs orally.

Nasogastric, gastrostomy, or intradialytic parenteral nutrition feeding may be necessary if these interventions are insufficient. *(Grade 1D)*

5.14 The dietary advice and nutritional products prescribed should minimise any deleterious effects on blood sugar or lipid levels. Regular review of the nutritional intervention should be maintained to monitor this. *(Grade 1D)*

5.15 In patients on active treatment of diabetes with insulin:

- Where there is a pre-dialysis glucose of <7 mmol/L, 20–30 g of a low glycaemic index carbohydrate is recommended at the beginning of the haemodialysis session to prevent further decline of blood glucose level. *(Grade 1D)*
- Capillary glucose should be assessed pre- and post-dialysis. *(Grade 1D)*
- The unit should ensure a hypoglycaemia treatment is accessible to patient at all times, including during travelling to and from the dialysis unit. *(Grade 2D)*

5.16 In case of hypoglycaemia:

- Appropriate rapid-acting carbohydrate treatment should be provided to take into account fluid, potassium and phosphate restrictions. *(Grade 1D)*
- 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)*
- Patients and staff should be educated in regard to the appropriate treatment of mild to moderate hypoglycaemia and hypoglycaemia unawareness. *(Grade 1D)*

5.17 Patients with gastroparesis are encouraged to have a small meal size but frequent intake. A low-fat and low-fibre meal is recommended to manage gastroparesis. *(Grade 1C)*

5.18 Clinicians should ensure that patients on maintenance haemodialysis with diabetes are aware that they are more likely to be able to maintain intra-dialytic weight gain (IDWG) at <4.5% of dry weight or <2 kg if they optimise their HbA1c. *(Grade 1D)*

5.19 Overweight/obese patients who are being considered for a kidney transplant should be encouraged to lose weight. Dietary counselling should be a calorie restrictive diet, making sure that the protein requirements for the patient are met (≥1.1 g/kg IBW). *(Grade 1D)*

5.20 Dietary counselling should also ideally include behavioural change strategies and increased physical activity. *(Grade 1B)*

5.21 All patients with an elevated BMI who may not be considered for transplantation if unable to lose weight through diet, exercise and behavioural change should be considered for bariatric surgery or weight-reducing medication. *(Grade 1C)*

5.1 Dietary recommendations and education

Recommendation 5.1:

Each Haemodialysis unit should have access to appropriate dietary expertise able to provide a holistic approach to the patient with diabetes. *(Grade 1D)*

Dietary advice should be personalised and include information on both diabetes and renal aspects of the diet. *(Grade 1D)*

Recommendation 5.1, above, recognises the need for a holistic and individualised approach to patient care, addressing the needs of both diabetes and renal care. Centres should have access to appropriate expertise in nutritional care and patient education.

Patients with diabetes who progress to ESRF and commence maintenance haemodialysis may have received dietary advice from a variety of sources. Information will have come from both the diabetes and renal team, from dietitians and from other health professionals. Each specialist area is likely to have its own agenda, whether aimed at improving HbA1c or reducing serum potassium, etc. This can lead to confusion for patients and ultimately poor adherence to the diet. Patients should identify achievable goals and lifestyle behaviours they want to modify.[1] Communication between specialities is essential to help reduce confusion and contradictory information being provided, a clear care plan should be developed, helping to achieve a holistic approach to patient care. It is therefore important that these patients are referred routinely to a registered dietitian who is qualified to assess their *overall* diet and offer appropriate, individualised advice.[2]

The way in which information is provided can aid understanding and adherence to the diet. A systematic review looking at education sessions for patients with diabetes on MHDx found improved knowledge and understanding about aspects of diabetic care including diet.[3] The review however only contained two small studies, including 207 patients, and the methodological design of the studies were felt to be poor. Another systematic review investigating interventions that enhance adherence to diet therapy in chronic diseases found several methods aided adherence, but no gold standard was identified.[4] Further studies are needed to identify the best way of educating/advising patients on dietary management.

5.2 Dietary recommendations for people with diabetes on maintenance haemodialysis

5.2.1 Overview

It is essential to document the patients' type of diabetes and the treatment they are receiving, including dietary management, insulin (type and dose) and/or oral hypoglycaemic agents (type and dose). Diet therapy for type 1 and 2 diabetes is different and this must be considered when providing additional dietary advice.[5]

Nutritional management for patients with stage 5 CKD receiving haemodialysis will consider energy, protein, potassium, phosphate, salt and vitamins.[6,7] There is little evidence or guidance as how to adapt dietary advice for those with additional dietary needs such as diabetes.

5.2.2 Rationale for specific dietary recommendations

Here, we provide the rationale for specific recommendations relating to dietary advice regarding consumption of macro- and micronutrients for people with diabetes on MHDx.

Recommendation 5.2:

It is recommended that patients on haemodialysis achieve an energy intake of 30–40 kcal/kg ideal body weight (IBW). *(Grade 1D)*

If a patient is aiming to lose weight appropriate individualised advice should be provided on energy requirements. *(Grade 1D)*

The required energy intake is dependent on gender, age and physical factors.[6–9] Consider the patient's ideal BMI in the context of recognised better outcomes for patients on haemodialysis with higher BMI[10] and maintain a BMI of at least >23.0 kg/m^2.[6,7] A BMI above the upper 50th percentile is optimal for improving survival in patients on MHDx.[11]

Patients with BMI >30 kg/m^2 may benefit from weight reduction, but the safety and efficacy of nutrient modification for weight loss need to be studied (see section 5.5 for further guidance on the management of obesity).

For patients with poor diabetic control who require nutrition support, consideration will need to be given to the balance between achieving improved glycaemic control and providing adequate calorie intake. This may need support from the diabetes team with regards to adjusting diabetes medications, to ensure acceptable blood glucose control is achieved with the increase calorie load (see Section 5.2 for further guidance on nutrition support).

Recommendation 5.3:

It is recommended that patients on haemodialysis achieve a protein intake of >1.1 g/kg IBW. *(Grade 1C)*

The recommendation that patients on haemodialysis should achieve a protein intake of >1.1 g/kg of IBW is supported by several national and international guidelines.[6–9]

Recommendation 5.4:

Dietary advice should be given for both dialysis and non-dialysis days to minimise significant glycaemic and caloric excursions. (Grade 1D)

Recommendation 5.5:

The type of diabetes the patient has should be identified and the dietary aims agreed. *(Grade 1C)*

Total energy should come from 50–60% carbohydrate, <30% fat and at least 15% from protein. *(Grade 1D, expert opinion)*

Protein and energy intake, including carbohydrates, of patients undergoing maintenance haemodialysis are known to be lower on dialysis days to non-dialysis days.[12] Education should be provided on insulin dose adjustment and carbohydrate counting, to allow for adjustment to treatment on these days. With regard to carbohydrate intake for people on insulin therapy:

- For patients on multiple daily insulin injections (basal bolus regimens) or continuous subcutaneous insulin infusions (insulin pumps), carbohydrate counting matching insulin doses to carbohydrate intakes improves glycaemic control.[5]
- For patients on fixed or biphasic insulin regimens, consistency in the quantity of carbohydrate at each meal, regular eating patterns and lower GI of foods are all beneficial and improve HbA1c levels.[5] A bedtime snack of <20 g carbohydrate may be required in some patients treated with biphasic insulin to prevent overnight or early morning hypoglycaemia.

Requirements for carbohydrate intake differ between type 1 diabetes and type 2 diabetes. Carbohydrate is the primary nutritional consideration for glycaemic control for people with type 1 diabetes, while weight management and total energy intake is the primary nutritional consideration for glycaemic control in people with type 2 diabetes.[5] Total carbohydrate intake is a strong predictor of glycaemic response and education on total carbohydrate intake, such as exchanges or portions, will help to achieve glycaemic control.[5] The type of carbohydrate also needs to be considered for people with type 2 diabetes: low GI diets reduce HbA1c by about 0.5% and are also advocated by Diabetes UK.[5]

According to the US National Kidney Foundation Kidney Disease Outcomes Quality Initiative™ (NKF KDOQI),[1] total energy intake should be:

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

As the protein requirements are increased for those on haemodialysis compared to non-dialysed CKD, the energy from non-protein sources should be reduced in order to prevent excess calorie intakes and weight gain if obesity is present. Based on 1.1g protein/kg IBW, at least 15% of total energy should be derived from protein.

Low K+ fruit, vegetables and carbohydrates with low-to-moderate GI should be encouraged to allow patients to achieve the recommended '5-a-day' fruit and vegetable portions. Low K+ dietary advice is indicated if serum K+ is ≥6.0mmol/L.[14]

Recommendation 5.6:

Low-potassium fruit, vegetables and carbohydrates with low-moderate glycaemic index should be encouraged to allow patients to achieve the recommended '5-a-day' fruit and vegetable portions. *(Grade 1D)*

K+ is found mainly in fruits, vegetables, pulses, legumes, nuts, milk and milk products.[15] Consumption of these foods is generally encouraged in the management of diabetes as they mostly have a low-to-moderate GI[16] and form part of healthy eating guidelines.[17]

More dietary freedom with fruits and vegetables is feasible if low K+ carbohydrate options (pasta, rice, noodles, bread, etc.) are encouraged in place of potatoes and other starchy root vegetables. Combining low K+ carbohydrates, fruit or vegetable options with appropriate cooking methods should allow the patient to achieve the '5-a-day' recommended in healthy eating guidelines.[17]

Insulin deficiency (and therefore hyperglycaemia) causes K+ redistribution and can result in hyperkalaemia[18]; this additional reason for optimal glycaemic control should be emphasised and explained to the patient. Other causes of hyperkalaemia such as medications, dialysis adequacy, recirculation, acidosis, constipation and spurious results should be investigated and corrected prior to advising on low potassium dietary advice.

Dietary advice should be tailored to the individual as a reduction in dietary K+ may be possible without addressing foods encouraged to optimise glycaemic control.

Recommendation 5.7:

Foods containing phosphate additives should be targeted prior to advice on reducing low glycaemic index foods e.g. wholegrain products and foods with high biological protein. *(Grade 1D)*

Foods containing phosphate additives should be targeted prior to advising on reducing low GI foods such as wholegrain products and foods with high biological protein. Low phosphate dietary advice should be provided to maintain serum phosphate 1.1–1.7 mmol/L.[19]

Low phosphate dietary advice has previously revolved around the reduction of dairy foods, eggs, seafood and nuts. These foods, however, are also sources of high biological protein and may be an essential part of the diet for this population. Phosphate additives in foods such as processed meats and meat products, cake mixes and fizzy drinks should be targeted first. Education on the management of diabetes may have already included reducing the amount of biscuits, cakes, desserts, etc., which can be high in phosphate additives.

Although wholegrain products are high in phosphate, this is unlikely to be absorbed due to the phytate content so should not be avoided. These products could in fact be encouraged and may help diabetes control due their low GI.

Dietary advice should be tailored to the individual as a reduction in dietary phosphate may be possible without addressing foods encouraged to optimise glycaemic control.

Recommendation 5.8:

A salt intake of <6 g/day is recommended. *(Grade 1C)*

A salt intake of <6 g/day is recommended for both dialysis and those with diabetes.[5] In addition, the importance of reducing salt as part of fluid management should be highlighted.[20]

Recommendation 5.9:

Oily fish should be recommended with caution for patients on haemodialysis, mainly because of vitamin A and phosphate content. *(Grade 2D)*

Oily fish should be recommended with caution for patients on haemodialysis, mainly because of vitamin A and phosphate content. Consumption of oily fish, rich in **ω**-3 unsaturated fats, is recommended at least twice per week in patients with diabetes.[5] Care should be taken for patients on dialysis as to the frequency and quantity of oily fish consumption, due to its Vitamin A content, which is not dialysed out and can become toxic. The phosphate content of the oily fish should also be considered and lower options such as those without bones should be advised for those patients requiring a low phosphate diet.

Recommendation 5.10:

It is recommended that patients on maintenance haemodialysis are prescribed a water-soluble vitamin supplement. *(Grade 2D)*

No randomised controlled trials exist to support the routine use of a multivitamin supplement other than for identified clinical need. However, the Dialysis Outcomes and Practice Patterns Study demonstrated a 16% reduction in mortality in MHDx patients taking water-soluble vitamins.[11] As such a supplement is cheap and easy to administer, and has minimal risk, it would seem prudent to recommend a water-soluble vitamin supplement to patients with diabetes on MHDx.

5.3 Nutrition support

5.3.1 Epidemiology and aetiology of protein energy wasting

PEW is considered to be a major cause of morbidity and mortality in haemodialysis (HD) patients.[7,21] Many studies indicate that it is more common in patients with diabetes vs. non-diabetes undergoing haemodialysis,[22,23] although the underlying mechanisms are not fully understood. While MHDx patients with or without diabetes share many risk factors for PEW, such as increased nutrient losses, acidosis, inadequate nutrient intake and increased catabolism,[24] additional risk factors in the MHDx population with diabetes may explain this increased prevalence, including increased muscle protein breakdown,[25] increased co-morbidities,[26] a higher prevalence of gastroparesis,[26] increased inflammatory cytokines,[27] and reduced taste acuity.[28]

Concerns regarding the glycaemic burden of nutritional interventions in patients with diabetes are less relevant in patients with malnutrition. In fact, a third of patients on dialysis with diabetes actually exhibit a state of 'burnt-out diabetes' in which frequent episodes of hypoglycaemia necessitate a reduction or discontinuation of diabetic medication.[29] A recent systematic review additionally expressed the opinion that a history of diabetes should not be a contra-indication for oral nutritional support.[30]

Although there is much guidance on the prevention and treatment of wasting in dialysis patients,[31] there is little specific to people with diabetes. It seems intuitively obvious that some approaches would remain the same such as ensuring adequate energy and protein intake and optimising dialysis prescription, though additional measures may need to be considered.

5.3.2 Identification of patients at risk of protein energy wasting

Recommendation 5.11:

All patients should be screened for protein energy wasting (PEW) on each admission to hospital. If no screening procedures are in place at dialysis units, a referral pathway and/or referral criteria should be in place to identify those at risk for appropriate referral to the dietitian for nutrition support.
(Grade 1D)

All inpatients should be screened for PEW on admission to hospital[32] and weekly thereafter.[8,32] However, it is important to note that many screening tools available in hospitals may not be specific enough to identify a dialysis patient at risk of PEW, particularly those using weight and BMI, as fluid changes can render them difficult to interpret.

Furthermore, it is difficult to meet the increased protein requirements from a standard hospital diet.[33] and many of the snacks/drinks on offer to patients in hospital are not appropriate for the renal patient with diabetes. Thus many patients would benefit from dietetic intervention and the provision of appropriate snacks and/or supplements from the outset.[34]

It has also been recommended that outpatients should be screened at their first clinic appointment[32] and/or at initiation of haemodialysis and 3–6 monthly thereafter.[8] Resources may not allow for this frequency of screening for all dialysis patients and therefore there should be procedures in place for appropriate referral to the renal dietitian if patients are identified by any member of the team to be at risk of PEW.

5.3.3 Initiation of nutrition support

Recommendation 5.12:

Initiation of nutrition support should be considered in those at risk of PEW. The indicators are the same in patients with and without diabetes. *(Grade 1C)*

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

- BMI <20 kg/m2.[8,24,35]
- Unintentional non-oedema weight loss >5–10% over 3–6 months.[8,35]
- <85% ideal body weight.[8]
- Subjective global assessment graded B/C or 1–5.[8]
- Intercurrent catabolic acute conditions which render normal nutrition impossible or which prevent adequate oral intake.[35]

Accelerated loss of lean body mass with no changes to BMI and body weight have been observed in incident dialysis patients with diabetes,[25] suggesting that anthropometric markers to estimate muscle mass should additionally be used in patients with diabetes. However, there is insufficient evidence to recommend this as routine and thus it would seem prudent to adopt the above guidelines for initiation of nutrition support for all dialysis patients with diabetes.

5.3.4 Routes of nutrition support

Recommendation 5.13:

Dietary counselling and oral nutrition support is the first-line treatment for patients who are unable to meet their nutritional needs orally.

Nasogastric, gastrostomy, or intradialytic parenteral nutrition feeding may be necessary if these interventions are insufficient. *(Grade 1D)*

It has been recommended that all malnourished haemodialysis patients should receive dietary counselling to discuss how to increase the calorie and protein content of their diets.[6] This may be through the use of diet and/or oral nutritional supplements (ONS). If a high fat diet is recommended to increase calorie intake, the use of foods high in monounsaturated and polyunsaturated fats should be considered to prevent the risk of hypercholesterolaemia, an important risk factor for cardiovascular disease (CVD). If intake is insufficient despite the use of ONS,[6,8,35] nasogastric feeding or gastrostomy feeding for long-term use should be considered. Jejunal feeding may be indicated for patients with a history of diabetic gastroparesis.[36]

A recent US national survey of 181,196 subjects found that patients with renal failure had a 1.6-fold increased risk of mortality post percutaneous endoscopic gastrostomy (PEG) placement.[37] Careful consideration should therefore be given when assessing a patient's suitability for a PEG.

Currently, when intensive dietary counselling, ONS and enteral feeding have failed, a course of intra-dialytic parenteral nutrition (IDPN) is recommended.[6,8,35] Although IDPN has been shown to improve energy and protein balance and nutritional parameters, it has not been shown to improve survival.[38] Special attention is required in patients with diabetes receiving IDPN including:

- Blood sugar monitoring before, during and 30 minutes after infusion of IDPN treatment.[39]
- Maintenance of serum glucose between 6–10 mmol/L.[40]
- Timely administration of insulin with the use of subcutaneous short acting insulin analogues being preferable to avoid post dialysis hypoglycaemia.[40]
- Glucose infusion of no more than 50–100 g per dialysis session.[41]
- A snack of 15–30 g carbohydrate within the last 30 minutes of dialysis to prevent hypoglycaemia post haemodialysis.[42]

5.3.5 Use of specific oral nutritional supplements and tube feeds

Recommendation 5.14:

Dietary advice and nutritional products prescribed should minimise deleterious effects on blood sugar or lipid levels. Regular review of the nutritional intervention should be maintained to monitor this. *(Grade 1D)*

European Best Practice Guidelines recommend products specifically formulated for dialysis patients, which take into account fluid and electrolytes. There are no specific recommendations for those with diabetes and there are no studies that have been carried out comparing products in this patient group to support any recommendations. It would be sensible to recommend oral nutritional supplements and tube feeds, which will have a less deleterious effect on both blood sugar and lipid levels, to reduce the risks of hyperglycaemia and CVD risk factors. In addition, it is important that patients 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.

5.3.6 Other strategies to optimise nutritional intake

It is essential to investigate causes of reduced oral intake and identify strategies to overcome these. In patients with diabetes, this may include optimisation of the treatment of diabetic gastroparesis,[43] achievement of normal glycaemic control[43] and evaluation and treatment of depression.

5.3.7 Gaps in knowledge and research recommendations on nutrition support

Key gaps in knowledge were identified as:

- Mechanisms of wasting in dialysis patients with diabetes.
- Efficacy of nutritional interventions in dialysis patients with diabetes.
- Optimal markers of nutritional status in dialysis patients with diabetes.

Further study is required to evaluate:

- The effects of different nutritional products on blood sugar levels, nutritional parameters and clinical outcomes in dialysis patients with diabetes.
- The effects of nutritional interventions on lean body mass in dialysis patients with diabetes.

5.4 Complications of diabetes

5.4.1 Management of mild hypoglycaemia

Recommendation 5.15:

In patients on active treatment of diabetes with insulin:

- Where there is a pre-dialysis glucose of <7 mmol/L, 20–30 g of a low glycaemic index carbohydrate is recommended at the beginning of the haemodialysis session to prevent further decline of blood glucose level. *(Grade 1D)*
- Capillary glucose should be assessed pre- and post-dialysis. *(Grade 1D)*
- The unit should ensure a hypoglycaemia treatment is accessible to patient at all times, including during travelling to and from the dialysis unit. *(Grade 2D)*

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

- Mild hypoglycaemia is defined as an episode of hypoglycaemia which can be managed by the patient themselves.
- Severe hypoglycaemia is defined as an episode of hypoglycaemia which requires assistance from another individual.

Dialysis patients are at risk of hypoglycaemia (see sections 4.2 and 6.1). Blood glucose levels tend to decline in non-diabetic patients during a haemodialysis session with the lowest during the third hour even though no hypoglycaemia may be reported.[44] Mean blood glucose concentrations post haemodialysis were also found to be significantly lower on dialysis vs. non-dialysis days[45] and 75% of hypoglycaemic events occurred within 24 hours of dialysis.[46]

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. 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 at the beginning of haemodialysis. Note that patients 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. 2. JBDS recommendations on managing hypoglycaemia.[47]

MANAGEMENT OF HYPOGLYCAEMIA IN HOSPITAL/SATELLITE DIALYSIS UNIT

Hypoglycaemia is blood glucose <4 mmol/L and may be asymptomatic

(If pre-dialysis blood glucose < 7 mmol/L, give 20–30g carbohydrate prior to dialysis)

Mild hypoglycaemia	Moderate hypoglycaemia	Severe hypoglycaemia
Sweaty	Tingling lips/fingers	Decreased consciousness
Shaky	Visual disturbance	Fitting
Pale/hungry	Anxious/restless (confusion)	Coma

HYPOGLYCAEMIA

If conscious, give:

- **3–4 Dextrose tablets (5 g/tablet) or**
- **1 1/2 Glucogel (10 g/tube) or**
- **1 cup Lucozade (90–120 mL) or 4 Jelly Babies/ 8 Jelly Beans (20g)**

If symptoms improve after 15 minutes and BGM >4 mmol/L, give 10–20g complex carbohydrate (biscuit, milk, toast or sandwich) and recheck blood glucose to ensure response

If symptoms do not improve after 15 minutes, repeat above treatment. If BGM still <4 mmol/L, call the Medical Team immediately

If unconscious, call the Medical Team:

Simultaneously also give:

- **20% Dextrose 100 mL** over 15 minutes
- **1 mg glucagon injection** (i.m. or s.c. if no i.v. access)

Once conscious, give 10–20 complex carbohydrate (biscuit, milk, toast or sandwich) and recheck blood glucose in 15 minutes

Ask the Medical Team to review medications/insulin before discharge

The treatment of hypoglycaemia in the inpatient/dialysis setting should be based on national guidance issued by the JBDS (Fig. 2).[47] For patients 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 1).[47]

Table 1. Examples of low GI sources of carbohydrate providing 10 g of glucose.[47]

- 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-dialysis needs to be considered to ensure it is safe for the patient 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 accessible to patient at all times, including during travelling to and from the dialysis unit.

5.4.2 Treating an episode of hypoglycaemia

Recommendation 5.16: In case of hypoglycaemia:

- Appropriate rapid-acting carbohydrate treatment should be provided to take into account fluid, potassium and phosphate restrictions. (Grade 1D)
- 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)
- Patients and staff should be educated in regard to the appropriate treatment of mild to moderate hypoglycaemia and hypoglycaemia unawareness. (Grade 1D)

In patients on MHDx the occurrence of a hypoglycaemic episode (<4 mmol/L with or without hypoglycaemic symptoms) should prompt active intervention and the use of 15–20 g rapid-acting glucose to treat a hypoglycaemia episode.[47,48]

Many of the rapid acting glucose preparations recommended for treating hypoglycaemia can be inappropriate for MHDx patients (e.g. 150 mL fruit juice or 100 mL cola drink). Not only do these treatments contribute toward significant fluid intake, especially if a patient 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 are:

Table 2. Recommended hypoglycaemia treatments

Source of rapid carbohydrate	Amount to provide 15 g carbohydrate
Lucozade® (Original)	90–120 mL
Dextrose tablets (5g per tablet)	3–4 tablets
Glucogel® (10g per tube)	1½ tubes
Jelly babies	4 (20ga)
Fruit pastilles	5 (19ga)
Jelly beans	8

[a]Estimated actual amount of carbohydrate.

5.4.3 Management of Gastroparesis

Recommendation 5.17:

Patients with gastroparesis are encouraged to have a small meal size but frequent intake. A low-fat and low-fibre meal is recommended to manage gastroparesis. *(Grade 1C)*

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.[49,50] Gastric emptying is significantly delayed in MHDx patients compared to control and this can affect nutritional status.[51] Gastric stasis will cause nausea, vomiting and dyspeptic symptoms such as early satiety, fullness or postprandial discomfort and bloating as well as anorexia.[50] These symptoms may lead to inadequate nutritional intake and add to the difficulty in controlling blood glucose.

The aim of dietetic management is to restore and maintain nutritional status as well as to improve glycaemic control. A suitable diet for the individual with gastroparesis is small, frequent, low in fibre and fat, with increased liquid nutrient intake; alcohol and carbonated drinks should be discouraged.[52]

A smaller meal size may also help to reduce gastric emptying time although meal size should be individualised according to patient's tolerance; fat in liquid form may be tolerated better[53]. There are no studies showing dietary fat delays gastric emptying in patients with gastroparesis. Therefore, using liquid fat could be a useful way to increase a patient's caloric intake.

A study comparing type 1 diabetes subjects with gastroparesis and healthy volunteers demonstrated an increment in gastric emptying rate and a reduction of post-prandial blood glucose dip in subjects receiving food of small particle size such as minced beef, blended pasta and carrots.[54] It is suggested to reduce particle size by adequate chewing of foods, or in severe cases, a puree or liquid diet is recommended.

Most studies have shown no difference in gastric emptying rate between soluble or insoluble fibre. Nevertheless, it is advised to reduce the amount of insoluble fibre in diet of patients with gastroparesis to prevent phytobezoar accumulation (these are found in raw vegetables, citrus fruits, celery, pumpkins, grapes, prunes and raisins),[55] perhaps with a low fibre and residue diet.[56] For patients with gastroparesis requiring enteral feeding, a post pyloric enteral feeding such as jejunal feed (placed surgically or endoscopically) is appropriate.

5.5 Fluid Management

Recommendation 5.18:

Clinicians should ensure that patients on maintenance haemodialysis with diabetes are aware that they are more likely to be able to maintain intra-dialytic weight gain (IDWG) at <4.5% of dry weight or <2 kg if they optimise their HbA1c. *(Grade 1C)*

Poor glycaemic control can lead to a vicious cycle of thirst and polydipsia, increasing problems with fluid management.[57] Therefore a patient with poorly controlled diabetes will continue to be at risk of a higher IDWG.[58] In the European Best Practice Guideline, maximum IDWG is defined as 2–5 kg (4–4.5% of dry weight).[6] However, the European Dialysis and Transplantation Nurses Association/European Renal Care Association in 2002 defined good IDWG as 1.5–2 kg (<4% of dry weight).[59]

5.6 Management of obesity

5.6.1 Obesity, type 2 diabetes and the haemodialysis patient

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

The results of numerous investigations on the impact of obesity on renal insufficiency conducted in recent years introduce certain dilemmas about their mutual agreement. Obesity within the dialysis population is even more confusing, as some research results suggest that obesity is positively correlated with survival of patients on dialysis, i.e. a higher BMI predicts a lower mortality rate, especially for extremely obese patients.[10,60] Also, it is confirmed that losing weight during the first year of haemodialysis treatment is associated with an increased mortality risk.[61] Haemodialysis patients with elevated BMI demonstrate a better nutritional status[62] and PEW is considered to be a major cause of morbidity and mortality in haemodialysis

patients.[7,21] The European Best Practice Guideline on Nutrition suggests that haemodialysis patients should maintain a BMI >23.0.[6]

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.[10] Malnutrition and reduced albumin levels were found to be independent predictors of mortality, whereas being overweight and obese did not show protective effects.[63]

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 actually protected in the short term, but later on are susceptible to higher mortality risks than people of normal body weight. A recent large study in Romania showed that overweight/obesity was associated with lower survival after 5 years whereas this association was not apparent after the first year.[64]

ESRF is ideally treated with renal transplantation.[65] Obesity contributes to increased risk of morbidity following surgery due to higher risk of co-morbidities such as cardiac, respiratory and metabolic diseases.[66] Obese transplant patients have been shown to experience adverse outcomes more commonly than transplant recipients of normal weight, including wound infections, delayed graft function, longer hospital stay, graft failure and cardiac disease.[67] For obese patients on dialysis treatment who are eligible for kidney transplantation, weight loss is advised to reduce obesity-related surgical complications and improve patient and graft survival after transplantation. In addition, many centres define BMI >30 kg/m^2 as an exclusion criterion for transplantation.[65] The Renal Association guidelines for assessing patients for transplantation suggest that obese patients with BMI >30 kg/m^2 present technical difficulties and are at increased risk of post-operative problems and therefore should be screened rigorously for cardiovascular disease.[68] Furthermore, patients with a BMI >40 kg/m^2 are less likely to benefit from transplantation.[68]

5.6.2 Weight loss interventions

Recommendation 5.19:

Overweight/obese patients who are being considered for a kidney transplant should be encouraged to lose weight. Dietary counselling should be a calorie restrictive diet, making sure that the protein requirements for the patient are met (≥1.1 g/kg IBW). *(Grade 1B)*

Recommendation 5.20:

Dietary counselling should also ideally include behavioural change strategies and increased physical activity. *(Grade 1B)*

5.6.2.1 Diets

The diet most successful in aiding weight loss in people with type 2 diabetes is still under debate. Guidelines for obesity in type 2 diabetes suggest that for overweight and obese patients 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.[5,69–73]

Very little research has been done on specific diets and weight reduction in patients on haemodialysis. One non-randomised trial following a 2-year weight management programme using low fat, exercise and orlistat demonstrated significant weight loss on patients on dialysis who were to undergo transplantation.[74] There are no other studies in the literature to our knowledge. 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 patients who are not considered transplant candidates the benefits of weight loss remain uncertain.[75]

5.6.2.2 Bariatric surgery

Recommendation 5.21:

All patients with an elevated BMI who may not be considered for transplantation if unable to lose weight through diet, exercise and behavioural change should be considered for bariatric surgery or weight-reducing medication. *(Grade 1C)*

The prevalence of obesity in MHDx patients is increasing,[76] which means more patients are being considered for bariatric surgery within the dialysis population; however, very limited data have been published with regards to CKD and especially patients are on dialysis. A recent systematic review of the effects of intentional weight loss in obese subjects with altered GFR, proteinuria or albuminuria found that only 13/31 studies were focused on the effects of bariatric surgery and only two of these studies included patients on haemodialysis.[77–79] The review did find that bariatric surgery reduced BMI or body weight in all studies (changes in BMI ranged from –4.5 kg/m^2 to –20.8 kg/m^2) and this was the most effective intervention for achieving long lasting weight loss in morbidly obese patients with CKD.[77] One study that focused on laparoscopic sleeve gastrectomy (including five patients undergoing haemodialysis) demonstrated a median weight decrease of 8.4 kg and an excess weight loss of 43% after 6 months; four of these patients were then eligible for a transplant.[79] Overall, there is very limited evidence of the benefits of bariatric surgery for weight loss in the CKD population, especially amongst patients on MHDx and current evidence base mainly relates to mainly observational reports and only a few randomised trials. A systematic review warns of the additional risk associated with these procedures in patients with CKD and the need for careful monitoring of fluid intake, kidney function and dialysis access.[77] They suggest large prospective controlled studies are needed to provide insights into safety and effectiveness of bariatric procedures in this population.

5.6.2.3 Weight reduction medication

See Recommendation 5.21, above

The NICE guideline on 'managing overweight and obesity in adults – lifestyle weight management services' 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.[80] From the systematic review described above, only five studies evaluated pharmacologic therapy alone or combined with another intervention, and only two of these studies included patients on haemodialysis.[77] Both studies involved a two year structured weight loss programme that included using orlistat, a calorie-restricted diet and aerobic exercise and patients in both achieved weight loss.[74,81]

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.

5.6.3 Gaps in knowledge and research recommendations

Key gaps in knowledge here are:

- The ideal BMI for dialysis patients with diabetes for improved long-term outcomes.
- Long-term outcomes of obesity within the haemodialysis population compared with the general population.
- Evidence to support the best dietary intervention to aid weight loss in the haemodialysis population with diabetes.
- Benefits of losing weight, tight glycaemic control on the dialysis population who are not to undergo transplantation.
- Risks/benefits of bariatric procedures and dietary recommendations within the haemodialysis population.
- Risks/benefits of medications for weight reduction within the haemodialysis population.

Research recommendations – studies are need to evaluate:

- The best approaches to aid weight loss in CKD population.
- The ideal BMI for those on dialysis who are or are not considered for renal transplantation.
- Effects of bariatric surgery within the haemodialysis population.
- Effects of weight management medication within the haemodialysis population.

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Section 6: Diabetes complications in haemodialysis patients

All recommendations

6.1 In managing patients with diabetes on maintenance haemodialysis, clinicians should be aware of the significantly increased risk of hypoglycaemia caused by:

- Poor or erratic nutritional intake.
- Reduced clearance of endogenous or exogenous insulin by the kidney and the liver.
- Decreased hepatic gluconeogenesis. *(Grade 1B)*

6.2 Patients with diabetes on maintenance haemodialysis should be adequately counselled on the increased risk of hypoglycaemia and that hypoglycaemia can occur with diminished classical symptoms. *(Grade 1B)*

6.3 Clinicians should counsel patients with diabetes and on maintenance haemodialysis about risk of hypoglycaemia on dialysis days, and consider reducing antihyperglycaemic therapy on dialysis days. (Grade 1D). NB: SEE RECOMMENDATION 5.15: Patients on maintenance haemodialysis on active treatment of diabetes with insulin or oral hypoglycaemic agent(s), should have capillary glucose assessed pre- and post-dialysis.

6.4 The heels of all patients with diabetes on haemodialysis should be protected with a suitable pressure relieving device during haemodialysis. *(Grade 2D)*

6.5 All patients with diabetes on dialysis should have their feet inspected at least weekly. *(Grade 2D)*

6.6 All patients with diabetes on dialysis should be considered high risk and should have regular review by the podiatry team. *(Grade 1C)*

6.7 Patients should have their feet screened three monthly using a locally agreed tool and by competent staff on the dialysis unit. *(Grade 1C)*

6.8 If the patient has an ulcer or there is any other concern the patient should be referred to the diabetic foot multidisciplinary team within one working day. *(Grade 1D)*

6.9 If the patient is on home dialysis it is the responsibility of the clinician in charge of their care (nephrologist or diabetologist) to ensure that the patient has an annual foot review and is attending review by the foot protection team. *(Grade 1D)*

6.10 Any patient presenting with a hot swollen foot should be referred to the diabetic foot team within 24 hours. *(Grade 1D)*

6.11 Patients with diabetes on MHDx approaching end of life or where a palliative care pathway has been agreed should be managed in accordance with Diabetes UK End of Life clinical care recommendations for patients with diabetes. Treatment and interventions should be focussed on symptoms. *(Grade 1D)*

6.1 Hypoglycaemia

6.1.1 The role of the kidney in glucose homeostasis

The role of the kidneys in glucose homeostasis is somewhat underappreciated.

- The kidneys are responsible for around 25% of glucose released into the plasma via gluconeogenesis In the fasting (post-absorptive) state and glucose utilisation by the kidneys in the fasting state accounts for around 10% of total body glucose utilisation.[1]
- About 180 g of glucose is filtered by the kidneys in 24 hours, most of which is reabsorbed via the proximal tubular SGLT2.[2]
- In type 2 diabetes, renal gluconeogenesis, glucose uptake and renal glucose reabsorption are all increased.[3]
- The relative increase in renal gluconeogenesis in patients with diabetes, is significantly greater than that seen in hepatic gluconeogenesis (300% vs. 30%).[1]

The kidney plays an important role in insulin metabolism in non-diabetic subjects:

- Insulin is freely filtered at the glomerulus, and 60% of renal insulin clearance relies upon glomerular filtration, whilst the remaining clearance is via the peritubular vessels.[4]
- Renal insulin clearance is around 200 mL/min, higher than normal GFR due to the contribution of renal tubular secretion.[5]
- Therefore, around 6–8 units of insulin are metabolised by the kidneys each day, equating to around a quarter of pancreatic insulin secretion in individuals without diabetes.

In patients with diabetes on exogenous insulin therapy, the contribution of the kidneys to insulin metabolism may be greater due to the lack of first pass metabolism by the liver when insulin is given subcutaneously. It is estimated that 30–80% of systemic insulin is metabolised by the kidney, and hence the kidneys role in metabolism of exogenous insulin is extremely important.[6]

6.1.2 Glucose homeostasis in CKD

CKD is an insulin resistant state. A number of mechanisms for this have been suggested, including the presence of uraemic toxins,[7] excess parathyroid hormone due to deficiency of active vitamin D (1,25 dihydroxyvitamin D),[8] or anaemia[9] leading to reduced skeletal muscle glucose uptake and diminished glycogen synthesis. Some of these hypotheses are evidenced by the fact that dialysis can significantly improve insulin sensitivity by removal of "uraemic toxins",[10] administration of active vitamin D may enhance insulin sensitivity,[11] and improved glucose uptake is seen following correction of anaemia with erythropoietin.[12]

A reduction in GFR may lead to changes in the way in which insulin is handled with increases in endogenous and exogenous insulin levels resulting in declining blood glucose concentrations.[13] The reduction in insulin clearance rate only becomes clinically significant at significant levels of renal impairment (eGFR <20 mL/min), as increased tubular uptake is able to compensate. Once GFR is sufficiently low, however, insulin degradation may become markedly reduced, leading to a significant risk of hypoglycaemia.[14]

Furthermore, a uremic environment reduces hepatic degradation of insulin and leads to accumulation of insulin.[15] Insulin secretion can also be impaired in uraemia. Metabolic acidosis seen in renal impairment may lead to suppression of insulin release,[16] and elevated parathyroid hormone may also lead to increased intracellular calcium, which blunts the release of insulin from pancreatic β-cells. Deficiency of active vitamin D may also be important in insulin secretion; administration of active vitamin D enhances insulin release.[11]

A true decline in blood glucose concentration in patients with progressive nephropathy may be a result of malnutrition.[17]

6.1.3 Insulin requirements in patients with diabetes and progressive renal disease

It is frequently noted that insulin requirements follow a biphasic course in progressive renal disease. In early stages of renal impairment, resistance to the effects of insulin predominates and may worsen, leading to a greater requirement for insulin.[18] In more advanced renal impairment, the loss of clearance of insulin will lead to falling insulin requirement, and subsequently, a higher risk of hypoglycaemia if insulin or sulfonylurea is not reduced.[14] In addition, uraemia induced reduction in calorie intake may also occur, leading to significant reductions in insulin requirement.

6.1.4 Hypoglycaemia in CKD

Recommendation 6.1:

In managing patients with diabetes on maintenance haemodialysis, clinicians should be aware of the significantly increased risk of hypoglycaemia caused by

- Poor or erratic nutritional intake.
- Reduced clearance of endogenous or exogenous insulin by the kidney and the liver.
- Decreased hepatic gluconeogenesis. *(Grade 1B)*

Recommendation 6.2:

Patients with diabetes on maintenance haemodialysis should be adequately counselled on the increased risk of hypoglycaemia and that hypoglycaemia can occur with diminished classical symptoms. *(Grade 1B)*

Recommendation 6.3:

Clinicians should counsel patients with diabetes and on maintenance haemodialysis about risk of hypoglycaemia on dialysis days, and consider reducing antihyperglycaemic therapy on dialysis days. *(Grade 1D)*

NB: see Recommendation 5.15: Patients on maintenance haemodialysis on active treatment of diabetes with insulin or oral hypoglycaemic agent(s), should have capillary glucose assessed pre- and post-dialysis.

Hypoglycaemia is the medical term for low blood glucose, and is defined as a blood glucose level of less than 4 mmol/L. Mild hypoglycaemia is defined as an episode of hypoglycaemia which can be managed by the patient themselves and severe hypoglycaemia is defined as an episode of hypoglycaemia which requires assistance from another individual.

Hypoglycaemia appears to be common among people both with and without diabetes and CKD (see section 4.2). In large epidemiological surveys, hypoglycaemia appears to occur twice as frequently amongst patients with CKD compared to people with normal renal function.[19]

Patients with diabetes on MHDx are likely to have suffered with diabetes for a long time and there may therefore be an increased likelihood of hypoglycaemic unawareness. This should be considered when managing hypoglycaemia on the haemodialysis unit as patients may present with blood glucose levels of <4mmol/L without symptoms and this requires medical attention.[20]

6.1.5 Effects of haemodialysis on glucose metabolism

In patients on MHDx, the intermittent nature of dialysis can make glucose metabolism difficult to manage. Haemodialysis may affect insulin secretion, clearance, and resistance as the result of periodic improvement in uraemia, acidosis, and phosphate metabolism. Glucose concentration in the dialysate may also influence glucose control, with lower glucose dialysates being associated with hypoglycemia.[21] Furthermore, dialysis may affect the clearance of antihyperglycaemic therapy such as insulin or SU. Therefore, glucose control on dialysis days may be very different to that on non-dialysis days, leading to unpredictable glucose levels, and glycaemic variability (see below).

See also Section 4.2

6.1.6 Glycaemic Variability

Patients with diabetes who have similar HbA1c may have significantly different plasma glucose profiles. Some have minimal glucose excursions with rare hypoglycaemia, whilst others have significant fluctuations in glucose, with frequent hypoglycaemia and marked post prandial peaks in glucose. The latter phenomenon is termed glycaemic variability.[22]

Haemodialysed subjects have greater glycaemic variability due to the fact that they are dialysed on alternate days and tend to have lower blood glucose values on dialysed days; their lowest readings are usually after their dialysis session, and blood glucose values are higher on non-dialysed days as glucose is accumulated in the blood despite receiving similar glucose-lowering medication. It has been proposed that to reduce this glycaemic variability, clinicians may need to identify subjects' glycaemic profile patterns and vary glucose lowering medications according to subjects' individual pattern/variability.[23]

Glycaemic variability can be described as "within-day", i.e. fluctuations within 24 hours, or "between-day" variability, due to differences in blood glucose control from day to day. For the reasons outlined above, patients on haemodialysis frequently have significant between day glycaemic variability, which may not be reflected in their HbA1c measurement. As HbA1c measures an average glycaemic exposure over about 90 days, it will not easily detect glycaemic variability and other methods may be necessary, such as CGM. With multiple glucose readings from CGM, the "mean amplitude of glucose excursions" (MAGE) may be calculated, which is a measure of within-day glucose variability.[24] MAGE reflects the difference between consecutive blood glucoses that are more than 1 standard deviation from the daily mean. For between-day variability, the "mean of daily differences" (MODD) – the average of the differences between blood glucoses measured at the same time on consecutive days – may be used.[25] There is a good degree of correlation between the two measures, and either may be used as a measure of glycaemic variability.

There is some evidence that long term glycaemic variability may be associated with vascular complications of diabetes. In the DCCT, glycaemic variability was associated with an increased risk of retinopathy and nephropathy over a nine year follow up in patients with type 1 diabetes.[26] There is some evidence that glucose variability may be associated with cardiovascular disease in patients with type 2 diabetes. In one study in patients with type 2 diabetes presenting with chest pain, patients with greater MAGE appeared to have greater severity of coronary artery disease.[27] Postprandial hyperglycaemia has been associated with increased carotid intima media thickening (CIMT),[28] and cardiovascular events.[29] Between-day variability of fasting glucose has been shown to be an independent predictor of cardiovascular mortality.[30]

Although glycaemic variability may be a risk factor for vascular complications of diabetes, the evidence for intervention to reduce glycaemic variability leading to reduced complications is not compelling. Some small intervention studies suggest that reduction in glycaemic variability using acarbose[31] or repaglinide[32] to specifically treat post prandial glucose levels may reduce incidence of myocardial infarction, or reduce CIMT. Glycaemic variability may also impact on a patient's quality of life, due to increased risk of hypoglycaemia.[33]

6.1.7 Glycaemic variability and hypoglycaemia in haemodialysis patients

For the reasons outlined above, glycaemic variability may be a particular problem in patients on haemodialysis. Studies using CGM in patients on haemodialysis with diabetes show wide and somewhat unpredictable swings in glucose levels. Some studies show lower glucose levels and a tendency to hypoglycaemia on dialysis days,[23] whilst others suggest a reduction in insulin requirement on the day after haemodialysis.[34] In studies which showed significantly increased hypoglycaemia on dialysis days, the hypoglycaemia tended to occur predominantly in the hours after dialysis had ceased.

6.1.8 Key research questions

- Is glycaemic variability (especially hypoglycaemia) in patients with diabetes on haemodialysis a major contributor to cardiovascular mortality and morbidity?
- Is CGM useful in managing patients with diabetes on haemodialysis, particularly with respect to reducing glycaemic variability and hypoglycaemia?
- What is the optimal insulin regimen for a patient on haemodialysis? Should insulin doses be varied on dialysis days and non-dialysis days?
- What is the role of non-insulin antidiabetic drugs in patients with diabetes on haemodialysis? Is there a role for metformin?

6.2 Diabetic foot disease in renal dialysis patients

ESRF and CKD 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 (OR, 4.2 [1.7–10])[35,36] and the risk of the development of a foot ulcer is temporally related to the onset of renal replacement therapy.[37] One study has shown that only 5% of all patients with diabetes on dialysis, independent of ethnicity, had no apparent risk factors for foot ulceration (either neuropathy, PAD or past foot ulcer).[38] 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 a patient is recumbent for prolonged periods of time.[39]

Recommendation 6.4:

The heels of all patients with diabetes on haemodialysis should be protected with a suitable pressure relieving device during haemodialysis. *(Grade 2D)*

Recommendation 6.5:

All patients with diabetes on dialysis should have their feet inspected at least weekly. *(Grade 2D)*

Recommendation 6.6:

All patients with diabetes on dialysis should be considered high risk and should have regular review by the podiatry team. *(Grade 1C)*

Recommendation 6.7:

Patients should have their feet screened three monthly using a locally agreed tool and by competent staff on the dialysis unit. *(Grade 1C)*

Recommendation 6.8:

If the patient has an ulcer or there is any other concern the patient should be referred to the diabetic foot multidisciplinary team within one working day. *(Grade 1D)*

Recommendation 6.9:

If the patient is on home dialysis it is the responsibility of the clinician in charge of their care (nephrologist or diabetologist) to ensure that the patient has an annual foot review and is attending review by the foot protection team. *(Grade 1D)*

A study from UK general practice has shown that major amputations are 7–8 times more likely in patients with diabetes and eGFR <30 mL/min compared with those with eGFR >60 mL/min.[35] Post-amputation mortality rates increase with the severity of renal disease, with patients with diabetes on dialysis having the most dismal prognosis.[40] Mortality rate post amputation is approximately 3-fold higher among dialysis patients.[41]

Podiatry input on dialysis units reduces the frequency of development and severity of diabetic foot complications among patients on MHDx,[42,43] and it is recommended that regular podiatry assessment (at least 3 monthly) is ensured for this high risk group.[44] This may need to be on dialysis units as this frail, multi-morbid population may have difficulty accessing community podiatry appointments.

Recommendation 6.10:

Any patient presenting with a hot swollen foot should be referred to the diabetic foot team within 24 hours. *(Grade 1D)*

The Charcot foot (Charcot neuropathic osteoarthropathy) is associated with very high morbidity and is frequently misdiagnosed as infection or venous thrombosis, or particularly in patients with renal disease, as gout. The diagnosis is often therefore delayed leading to worsening structural damage, secondary ulceration, osteomyelitis and potentially avoidable limb loss.[45]

The risk of the development of an acute Charcot foot also associates with renal disease – in one series 30% were on renal replacement therapy.[46] 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 possibly 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.[47]
- However, patients on renal replacement therapy may tolerate this poorly due to changing peripheral oedema.
- Other methods of offloading (for example removable cast and wheelchair use) may be required.

6.3 End of life care in patients with diabetes on maintenance haemodialysis

Recommendation 6.11:

Patients with diabetes on MHDx approaching end of life or where a palliative care pathway has been agreed should be managed in accordance with Diabetes UK End of Life clinical care recommendations for patients 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.[48–53] This is more common in older people, those with chronic or progressive co morbidities and people who are becoming increasingly dependent.[54]

Care provision and links with other specialist teams, including palliative care teams, may be warranted at this time.[55] Clear guidance for the management of end of life care in patients 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 so that hypoglycaemia can be avoided. Conversely it is important that insulin treatment is not stopped completely in patients with Type 1 diabetes as this can lead to DKA and severe dehydration. Early liaison with the diabetes specialist team is recommended when planning care for these patients.

Blood glucose monitoring can be minimised to only once daily with a glycaemic targets of 6–15 mmol/L without diabetes symptoms, in those receiving insulin treatments. 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 patient or there is lack of capacity, the carer. Teams need to ensure that the patients' wishes are paramount when planning end of life care and effective communication with the patient, their relatives or carer and GP is in place.[55,56]

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