Haemodialysis-induced hypoglycaemia and glycaemic disarrays

Masanori Abe and Kamyar Kalantar-Zadeh

Abstract | In patients with diabetes receiving chronic haemodialysis, both very high and low glucose levels are associated with poor outcomes, including mortality. Conditions that are associated with an increased risk of hypoglycaemia in these patients include decreased gluconeogenesis in the remnant kidneys, deranged metabolic pathways, inadequate nutrition, decreased insulin clearance, glucose loss to the dialysate and diffusion of glucose into erythrocytes during haemodialysis. Haemodialysis-induced hypoglycaemia is common during treatments with glucose-free dialysate, which engenders a catabolic status similar to fasting; this state can also occur with 5.55 mmol/l glucose-containing dialysate. Haemodialysis-induced hypoglycaemia occurs more frequently in patients with diabetes than in those without. Insulin therapy and oral hypoglycaemic agents should, therefore, be used with caution in patients on dialysis. Several hours after completion of haemodialysis treatment a paradoxical rebound hyperglycaemia may occur via a similar mechanism as the Somogyi effect, together with insulin resistance. Appropriate glycaemic control tailored for patients on haemodialysis is needed to avoid haemodialysis-induced hypoglycaemia and other glycaemic disarrays. In this Review we summarize the pathophysiology and current management of glycaemic disarrays in patients on haemodialysis.

Abe, M. & Kalantar-Zadeh, K. *Nat. Rev. Nephrol*. **11**, 302–313 (2015); published online 7 April 2015; corrected online 27 April 2015; doi:10.1038/nrneph.2015.38

Introduction

Type 2 diabetes mellitus (T2DM) is one of the leading causes of chronic kidney disease (CKD) and end-stage renal disease (ESRD) in developed and developing countries.[1] In the USA, New Zealand, Japan and some other Asian countries, T2DM accounts for nearly 50% of patients on incident dialysis.[2,3] The disease has been described as a condition of dysglycaemia, which occurs mostly in the form of hyperglycaemia. However, two other components of dysglycaemia—hypoglycaemia and glucose variability—are now also considered to be clinically relevant as they each contribute to the overall risk of adverse diabetes-related outcomes.[4] Hypoglycaemic events can be exceptionally serious, even life-threatening, and can make glycaemic control of diabetic patients challenging. Hence, whereas hyperglycaemia was traditionally the main focus of attention, contemporary medicine considers the occurrence of hypoglycaemia an even more substantial challenge in the management of T2DM.

Optimum glycaemic control of diabetic patients with CKD is a topic of considerable uncertainty and confusion.[5] In diabetic patients with ESRD receiving chronic haemodialysis, several large observational studies have highlighted the risks associated with low haemoglobin A_{1c} (HbA_{1c}) levels. Data from these studies suggest that not only hyperglycaemia, but also low glucose levels (<5.55 mmol/l) are associated with increased mortality risk.[6–8] Maintaining consistent glycaemic control is difficult in patients with ESRD because the disease causes many changes in glucose metabolism, insulin resistance, secretion and degradation, whereas haemodialysis treatment results in changes to drug metabolism. Moreover, wide daily intrapatient variability in nutritional intake, adherence to antidiabetic agents and cognitive function linked with the dialysis schedule is not uncommon. In this Review, we discuss the pathophysiology and management of haemodialysis-induced hypoglycaemia and hyperglycaemia in patients with diabetes.

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Competing interests
K.K.Z. has received honoraria from Abbott, Abbvie, Amgen, Fresenius, Shire and Vifor. M.A. declares no competing interests.

Haemodialysis-induced hypoglycaemia

Hypoglycaemia occurs not infrequently in patients with ESRD, especially during haemodialysis sessions, and is particularly common in those with diabetes mellitus.[9–11] Factors that are associated with an increased risk of haemodialysis-induced hypoglycaemia include use of glucose-free dialysate, glucose loss during dialysis, decreased renal gluconeogenesis and alterations in metabolic pathways (Figure 1).

Inclusion of glucose in dialysate

Use of glucose-containing and glucose-free dialysates in patients with diabetes has changed considerably over time (Box 1). In the USA dialysates that contain 5.55 mmol/l glucose are currently the most commonly used, whereas 11.10 mmol/l glucose-containing dialysates seem to have fallen out of favour.[12] Similarly in the majority of European countries, the most frequently used glucose concentration

Key points

- In patients with diabetes undergoing haemodialysis, both extremely high and low glycaemic levels are associated with increased morbidity and shortened survival owing to vascular and diabetic complications and malnutrition
- Factors that are associated with an increased risk of hypoglycaemia in patients on haemodialysis include decreased renal gluconeogenesis, deranged metabolic pathways (including altered metabolism of medications) and decreased insulin clearance
- Glucose loss to the dialysate and diffusion of glucose into erythrocytes during haemodialysis are also associated with haemodialysis-induced hypoglycaemia
- Inclusion of glucose in the dialysate is important to prevent haemodialysis-induced hypoglycaemia; use of glucose-free or low-glucose dialysates should be avoided in patients with diabetes
- After the completion of a haemodialysis session, a paradoxical hyperglycaemia may ensue via a mechanism similar to the Somogyi effect, together with insulin resistance and insulin removal by the dialyzer
- Appropriate glycaemic control tailored for diabetic patients is required to avoid haemodialysis-induced hypoglycaemia and other glycaemic disarrays

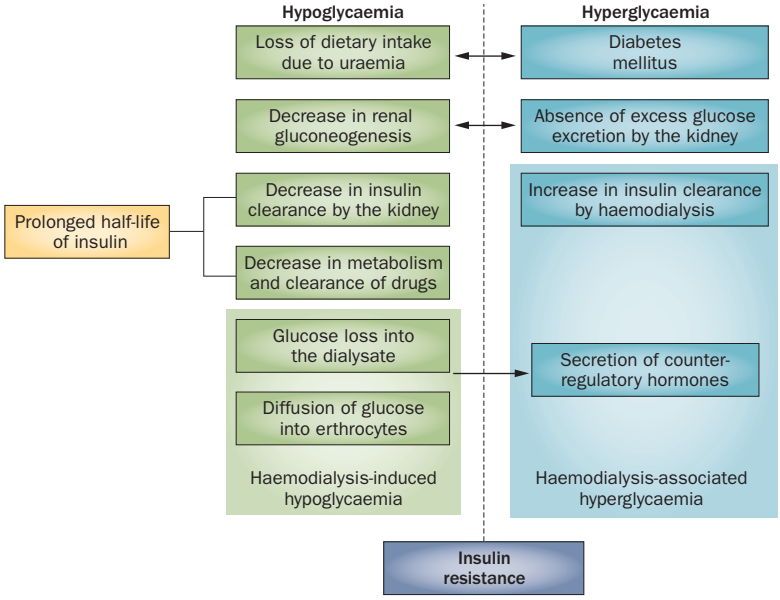

Figure 1 | Factors associated with hypoglycaemia and hyperglycaemia in patients with end-stage renal disease.

is 5.55 mmol/l. In some European countries, however, glucose-free dialysate is used, mainly because of concerns regarding potential bacterial and fungal contamination as well as economic considerations.[13] In Japan, dialysates that contain 5.55 mmol/l glucose are most commonly used, but use of 6.94 mmol/l glucose and 8.33 mmol/l glucose dialysates is increasing.

When a glucose-free dialysate is used asymptomatic hypoglycaemia (defined as serum glucose <4 mmol/l) occurs in approximately 40% of patients with or without diabetes.[10] Data on dysglycaemia in patients dialysed using 5.55 mmol/l glucose solution are inconsistent. In one study no episodes of haemodialysis-induced hypoglycaemia were reported in 21 nondiabetic patients, whereas one of 18 diabetic patients developed hypoglycaemia.[10,14] A crossover study that included 20 diabetic patients showed that more patients had hypoglycaemic episodes when dialysed using a dialysate with 5.55 mmol/l glucose than when a dialysate with 11.10 mmol/l glucose was used.[11] A subsequent study reported hypoglycaemia in only one of 21 diabetic and none of 21 nondiabetic patients treated with a 5 mmol/l glucose-containing dialysate, whereas hypoglycaemia occurred in five of 20 diabetic and five of 20 nondiabetic patients treated with glucose-free dialysate.[15] We found that a 5.55 mmol/l glucose-containing dialysate was preferable to a glucose-free dialysate for preventing acute haemodialysis-induced hypoglycaemia and maintaining good glycaemic control in 31 diabetic and 18 nondiabetic patients.[16] In both groups hypoglycaemic episodes occurred more frequently with the glucose-free dialysate than with the glucose-containing dialysate despite a fairly low blood flow rate (200 ml/min) and a constant 500 ml/min dialysate flow rate consistent with the typical dialysis treatment setup in Japan.[16]

Haemodialysis treatment using 5.55 mmol/l glucose-containing dialysate is currently considered standard procedure in many dialysis clinics. Typically, if the plasma glucose level exceeds 5.55 mmol/l during a haemodialysis session using this dialysate, glucose is expected to diffuse from the blood to the dialysate across the concentration gradient. However, in many patients the glucose level at the post-dialyser site decreases to <5.55 mmol/l owing to the counter-current passage of plasma through the dialyser.[16] If the plasma glucose level at the pre-dialyser site exceeds 8.33 mmol/l, plasma glucose levels at the post-dialyser site should not decrease below 5.55 mmol/l; however, in the case of a mean plasma glucose level of 6.94 ± 0.83 mmol/l at the pre-dialyser site, glucose levels might decrease to 5.33 ± 0.22 mmol/l at the post-dialyser site.[16]

Takahashi *et al.* demonstrated that in nondiabetic volunteers undergoing haemodialysis using 5.55 mmol/l glucose-containing dialysate, plasma glucose levels decreased from 6.57 mmol/l at the pre-dialyser site to 5.47 mmol/l at the post-dialyser site (a differential of almost 1.11 mmol/l).[17] Furthermore, plasma glucose concentrations at the post-dialyser site after 2 h (5.29 mmol/l) and 4 h (5.1 mmol/l) of dialysis treatment were significantly lower than the glucose concentrations of the dialysate at 2 h (5.83 mmol/l) and at 4 h (5.76 mmol/l). The researchers speculated that these decreases in blood glucose levels might be caused by the diffusion of plasma glucose into erythrocytes; changes in the cytoplasmic pH of erythrocytes during haemodialysis result in accelerated anaerobic metabolism and increased glucose consumption. Use of glucose-free or low-glucose dialysate is, therefore, associated with a greater risk of developing hypoglycaemia than is use of high-glucose (≥5.55 mmol/l) dialysate. According to this rationale, dialysis fluids that contain 11.10 mmol/l glucose are less likely to be associated with hypoglycaemic episodes than are those that contain 5.55 mmol/l glucose.[11]

Metabolic effects of glucose-free dialysate

Significant increases in the plasma levels of β-hydroxybutyrate and acetoacetate are more likely to occur after haemodialysis with a glucose-free dialysate than with a glucose-containing dialysate.[18] This finding suggests that when a glucose-free dialysate is used, the body tries to maintain an adequate blood glucose

Box 1 | The history of glucose-containing dialysate

Early in the history of haemodialysis, inclusion of glucose in the dialysate was important to ensure effective osmotic ultrafiltration, which was the main method of volume removal by the 1960s. At this time, the major osmoles were sodium and glucose, and the glucose concentration of the dialysate was as high as 99.9 mmol/l.[12] Later, when ultrafiltration by hydrostatic pressure or reverse osmosis was found to be more effective than osmotic ultrafiltration, the glucose concentration of dialysate was markedly decreased and many dialysis units eventually switched to using glucose-free dialysates. Initially concerns were raised that use of glucose-free dialysates might result in hypoglycaemia, along with an increased likelihood of a catabolic state and greater loss of amino acids. On the other hand, some argued that inclusion of any glucose in the dialysate might increase the risks of hypertriglyceridaemia and dialysate contamination as well as increase manufacturing costs.[138] Hence, until the early 1990s, glucose was not included in dialysate fluid in many parts of the world. Opinion changed again, however, when high blood flow rates against the continuous flow of glucose-free dialysate through the dialyser were found to result in rapid loss of serum glucose across semi-permeable dialysis membranes, leading in turn to frequent episodes of moderate to severe hypoglycaemia.[9–11,17,139–141] This haemodialysis-induced hypoglycaemia was thought to pose additional risks of adverse outcomes, particularly in asymptomatic patients and/or those who sleep during haemodialysis sessions, as their hypoglycaemia might go unnoticed. Consequently, dialysates containing 5.55 mmol/l and 11.1 mmol/l glucose were approved for manufacture and became commercially available in most countries. A trend now exists to replace 11.1 mmol/l glucose dialysate fluids with 5.55 mmol/l glucose dialysates and to reconsider the use of glucose-free dialysates despite the known risks.

concentration by changing to a more catabolic state of gluconeogenesis and glycogenolysis. Such a mechanism explains why levels of lactate and pyruvate—substances important for gluconeogenesis—are decreased under such circumstances.

Energy is provided for gluconeogenesis by the substantial increases in levels of β-hydroxybutyrate and acetoacetate that occur secondary to fatty acid oxidation.[19] Several studies that investigated the association between these metabolic effects and glucose-free dialysates have shown that patients enter a catabolic state similar to the fasting state.[20] During a glucose-free dialysis session, 15–30 g of glucose is removed from the patient and this loss can result in clinically manifest or undiagnosed hypoglycaemia.[10,14,20–23] The drop in glucose concentration is counteracted by endogenous glucose production, which occurs through gluconeogenesis and glycogenolysis. Patients without diabetes can usually tolerate this catabolic state, whereas those with malnutrition or a weakened physical state often cannot and are at increased risk of hypoglycaemia. Diabetic patients on dialysis, particularly those who are receiving long-acting insulin or oral hypoglycaemic agents, are at particularly high risk of hypoglycaemia.

Frequently recurring episodes of hypoglycaemia in diabetic patients result in decreased neurohumoral responses to low blood glucose levels and diminished clinical manifestations of hypoglycaemia.[24] A single episode of hypoglycaemia can cause a generalized reduction of the neuroendocrine and symptomatic response to subsequent episodes even in nondiabetic individuals.[25] In animals, long-term maintenance of hypoglycaemia increases the capacity of brain cells for glucose uptake, and a similar mechanism could explain the asymptomatic nature of hypoglycaemia in some patients with diabetes.[26] Frequent recurrence of hypoglycaemic episodes—despite their asymptomatic nature—might increase the risk of progressive cognitive impairment in patients with diabetes.[27–29]

Use of glucose-containing dialysate reduces anaerobic metabolism during haemodialysis and interrupts the vicious cycle that eventually leads to hypoglycaemia in the short-term and neurological deficits in the long-term.[27–29] Although not yet unequivocally proven, it can be argued that using a standard physiological concentration of glucose (at least 5 mmol/l) in the dialysate will minimize these metabolic effects. Clinicians who treat nondiabetic patients on haemodialysis must be careful when using glucose-free dialysate because silent hypoglycaemia can occur; the glucose content of the haemodialysis solution is a major consideration in treatment. The addition of glucose to dialysate might help to maintain energy balance by decreasing the risk of hypoglycaemia and to limit oxidative stress by maintaining normal activity of the hexose monophosphate cycle in erythrocytes, which delivers free radical scavengers but does not reduce the negative effect of haemodialysis treatment on protein metabolism.[22,23,30,31] Moreover, increasing extracellular osmolality by augmenting the dialysate sodium concentration decreases fluid loss to the intracellular compartment, leading to a reduced risk of dialysis-associated hypotension.[10,14,32] When glucose is added to the dialysate, the resulting increase in extracellular osmolality can be expected to have a similar effect.

Hyperinsulinaemia

Hyperinsulinemia owing to dialysis with 11.10 mmol/l glucose-containing dialysate might induce the production of pro-inflammatory cytokines and promote insulin resistance.[13] As hyperglycaemia is associated with increased levels of proinflammatory cytokines, it seems logical to suspect that exposure of patients to such dialysate may be a causative factor in the inflammation associated with ESRD. However, additional research is needed to substantiate this hypothesis and to investigate the potential effects of hyperinsulinaemia on patient survival.

Decreased renal gluconeogenesis

Endogenous production of glucose by glycogenolysis and gluconeogenesis maintains plasma glucose levels during the fasting state.[33–35] The kidney has sufficient gluconeogenic enzyme and glucose-6-phosphate activity to generate substantial amounts of glucose via endogenous production; renal glucose production is thought to principally occur though gluconeogenesis rather than glycogenolysis.[36] The kidney contributes to approximately 40% of gluconeogenesis and accounts for up to 20% of all glucose production.[37] In normal kidneys, the poorly perfused, relatively hypoxic medulla is the site of considerable glycolysis, whereas the cortex is the preferred site for gluconeogenesis. Decreased nephron mass and kidney dysfunction lead, therefore, to a reduction in renal gluconeogenesis.[38,39]

Various stimuli, including fasting, hypoglycaemia and diabetes, can alter renal gluconeogenesis. Patients with

T2DM and normal kidney function show an increase in glucose production of up to 300%, which is usually contributed equally by hepatic and renal beds.[40,41] Renal gluconeogenesis contributes to maintenance of normal glucose levels in the fasting state; hypoglycaemia promotes renal gluconeogenesis by increasing the renal uptake of circulating gluconeogenic substrates.[35] In patients on dialysis, however, the role of gluconeogenesis in the maintenance of glucose homeostasis might diminish as a result of thinning of the renal cortex. Such a reduction in gluconeogenesis might explain why hypoglycaemic episodes tend to be prolonged in patients on dialysis.

A spontaneous resolution of hyperglycaemia and treatment-independent normalization of HbA_{1c} levels, known as 'burnt-out diabetes', is commonly observed in diabetic patients on dialysis (Figure 2).[42–45] In a 2007 study, up to one-third of 23,618 diabetic patients receiving dialysis had normal HbA_{1c} levels (<6%), many of these patients likely had burnt-out diabetes.[7] Frequent hypoglycaemic episodes may result in the discontinuation of insulin and oral antidiabetic agents in patients on dialysis.[7,44,45] Moreover, patients who lack viable kidney tissue may inherently be more prone to hypoglycaemic episodes, potentially explaining the occurrence of 'burnt-out diabetes' in patients with ESRD.

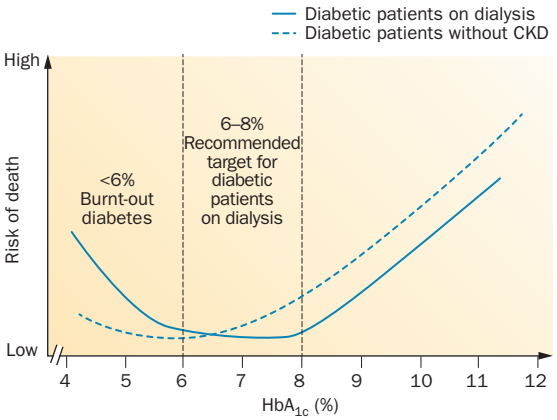

Figure 2 | HbA_{1c} levels and mortality in patients on dialysis. Approximately one-third of diabetic patients receiving haemodialysis have an average HbA_{1c} level of <6%, referred to as 'burnt-out diabetes'. The optimal target HbA_{1c} range for patients on dialysis seems to differ from that of the general population. Abbreviation: HbA_{1c}, haemoglobin A_{1c}. Permission obtained from Wiley © Rhee, C. M. *et al*. *Semin. Dial*. **27**, 135–145 (2014).

Effects of antidiabetic agents and other therapies

Patients with impaired kidney function are prone to hypoglycaemia owing to a delay in the metabolism and excretion of insulin, which is partly degraded in the kidney, and of oral hypoglycaemic agents. Two reports have suggested that most emergency cases of severe hypoglycaemia in patients with substantially impaired kidney function occur in those who have received sulphonylureas or insulin therapy.[46,47] Dose adjustments of antidiabetic agents are, therefore, recommended in patients with CKD (Table 1).[48–55]

Metformin is contraindicated in patients with ESRD and in patients with CKD who have a glomerular filtration rate (GFR) <30 ml/min/1.73 m^2.[56] Among the oral hypoglycaemic agents, sulphonylureas stimulate insulin secretion and tend to induce prolonged hypoglycaemia. Some of these medications are contraindicated or should be used sparingly in patients on dialysis.

The meglitinides repaglinide, mitiglinide and nateglinide are rapid, short-acting insulinotropic sulphonylurea receptor ligands. As use of repaglinide or mitiglinide is rarely accompanied by hypoglycaemia, these agents are attractive therapeutic options for patients on dialysis. However, mitiglinide is not currently marketed worldwide. In contrast to the other meglitinides, nateglinide is contraindicated in patients on dialysis. Nateglinide metabolites have insulin secretion properties and the prolonged half-life of this agent in patients with advanced CKD can result in hypoglycaemic episodes.[49]

As the thiazolidinediones pioglitazone and rosiglitazone are completely metabolized by the liver no dose adjustments are needed for patients on dialysis. Use of these agents is, however, generally avoided in patients with CKD owing to adverse effects including refractory fluid retention, hypertension and increased fracture risk.[55,57] Thiazolidinediones are contraindicated for patients on dialysis in Japan as they can increase fluid retention and have been associated with heart failure.[49]

Use of α-glucosidase inhibitors is rarely accompanied by hypoglycaemia and in Japan these agents are administered to patients on dialysis without dose adjustment with careful administration.[49,58] Our group found that treatment with voglibose was effective and safe in patients on haemodialysis.[58] Nevertheless, Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines recommend that acarbose and miglitol should be avoided in patients on dialysis because plasma levels of these agents can increase in patients with CKD and such accumulation in patients with serum creatinine levels >176.8 μmol/l could potentially lead to liver failure.[50,52]

Dipeptidyl peptidase 4 (DPP-4) inhibitors offer potential advantages for patients with CKD as they are associated with a low risk of hypoglycaemia. Efficacy and safety of these agents has been reported in patients undergoing haemodialysis.[59–61] All of the currently available DPP-4 inhibitors can be used in patients with CKD, but sitagliptin, saxagliptin, and alogliptin require dose adjustment based on GFR. Linagliptin does not require dose adjustment based on kidney function. Sodium-glucose cotransporter 2 inhibitors are now available but should not be used in patients on dialysis because their efficacy is dependent on GFR and they are ineffective in anuric patients.

Intensive insulin therapy can help to achieve target HbA_{1c} levels but also increases the risk of severe hypoglycaemia in diabetic patients.[62,63] Total insulin requirements decrease by 25% when GFR falls below 50 ml/min/1.73 m^2 and by a further 50% when it falls below 10 ml/min/1.73 m^2.[51,64,65] Upon initiation of dialysis, peripheral insulin resistance may improve, further reducing insulin requirements.[66] As clearance and catabolism of insulin decreases, the

Table 1 | Dose adjustments for antidiabetic agents in patients with CKD[49–53]

Class	Drug(s)	Dose adjustment(s)
Insulin	—	Reduce dose as GFR decreases
GLP-1 receptor agonists	Exenatide	No dose reduction if GFR ≥50 ml/min/1.73 m² Use with caution if GFR 30–50 ml/min/1.73 m² Contraindicated if GFR <30 ml/min/1.73 m²
	Liraglutide	No dose reduction necessary
Biguanides	Metformin	No dose reduction if GFR ≥45 ml/min/1.73 m² Use with caution if GFR 30–44 ml/min/1.73 m² Contraindicated if GFR <30 ml/min/1.73 m²
Sulphonylureas	Glipizide	No dose reduction necessary
	Glimepiride	Initiate conservatively at 1 mg daily if GFR <60 ml/min/1.73 m²
	Glyburide	Contraindicated if GFR <60 ml/min/1.73 m²
Meglitinides	Repaglinide	No dose reduction if GFR ≥30 ml/min/1.73 m² Initiate at 0.5 mg with meals if GFR <30 ml/min/1.73 m²
	Nateglinide	Initiate at 60 mg with meals if GFR 30–59 ml/min/1.73 m² Contraindicated if GFR <30 ml/min/1.73 m²
	Mitiglinide*	Use with caution if GFR <60 ml/min/1.73 m²
Thiazolidinediones	Rosiglitazone	No dose reduction necessary
	Pioglitazone	No dose reduction necessary 15–30 mg daily has been used in patients on dialysis
α-Glucosidase inhibitors	Acarbose‡	Use with caution if GFR 30–59 ml/min/1.73 m² Contraindicated if GFR <30 ml/min/1.73 m²
	Miglitol‡	Use with caution if GFR 25–59 ml/min/1.73 m² Contraindicated if GFR <25 ml/min/1.73 m²
	Voglibose*‡	No dose reduction if GFR ≥30 ml/min/1.73 m² Use with caution if GFR <30 ml/min/1.73 m²
DPP-4 inhibitors	Sitagliptin	100 mg daily if GFR ≥50 ml/min/1.73 m² 50 mg daily if GFR 30–49 ml/min/1.73 m² 25 mg daily if GFR <30 ml/min/1.73 m²
	Saxagliptin	5 mg daily if GFR ≥50 ml/min/1.73 m² 2.5 mg daily if GFR <50 ml/min/1.73 m²
	Vildagliptin*	Use with caution if GFR <60 ml/min/1.73 m²
	Linagliptin	No dose reduction necessary
	Alogliptin	25 mg daily if GFR ≥50 ml/min/1.73 m² 12.5 mg daily if GFR 30–49 ml/min/1.73 m² 6.25 mg daily if GFR <30 ml/min/1.73 m²
SGLT2 inhibitors	Canagliflozin	100–300 mg if GFR ≥60 ml/min/1.73 m² 100 mg if GFR 45–59 ml/min/1.73 m² Contraindicated if GFR <45 ml/min/1.73 m²
	Dapagliflozin	Contraindicated if GFR <60 ml/min/1.73 m²

*Not available in the USA. ‡Available in Japan for patients on dialysis. Abbreviations: CKD, chronic kidney disease; DPP-4; dipeptidyl peptidase 4; GFR, glomerular filtration rate; GLP-1, glucagon-like peptide-1; SGLT2, sodium–glucose cotransporter 2.

metabolic effects of short-acting and long-acting insulin preparations persist for longer periods and the potential for symptomatic hypoglycaemia increases. Moreover, rapid glycaemic control through intensive insulin therapy may worsen retinopathy and neuropathy.[63] To prevent hypoglycaemia, education in self-monitoring of blood glucose level should be provided to patients in addition to appropriate hypoglycaemia management.[67]

Some medications, including the β-blocker propranolol, salicylates and disopyramide, are common causes of hypoglycaemia. Additional precipitating events include alcohol consumption, sepsis, chronic malnutrition, acute caloric deprivation, gastroparesis, concomitant liver disease and congestive heart failure.[68,69] The risk of hypoglycaemia is increased in diabetic patients on dialysis who are receiving β-blockers as these agents impair gluconeogenesis and mask symptoms of hypoglycaemia.

Hyperglycaemia and other glucose disarrays

Anuric patients with ESRD cannot excrete excess plasma glucose in their urine and are therefore characterized by postprandial hyperglycaemia. Factors that are associated with haemodialysis-associated hyperglycaemia and other glucose disarrays in patients with ESRD include insulin resistance, removal of insulin by haemodialysis and secretion of counter-regulatory hormones (Figure 3).

Insulin resistance

Patients with ESRD often show insulin resistance, as evidenced by a lowered sensitivity to the hypoglycaemic effect of exogenous insulin.[70] Hepatic glucose production is, however, not increased and is in fact normally suppressed by insulin in patients with ESRD, suggesting that insulin resistance occurs in a peripheral site in these patients. As <2% of the glucose load is disposed of in adipose tissue, the most likely main site of insulin resistance is muscle tissue.[71] In patients with ESRD, insulin resistance is associated with degradation of muscle proteins via the ubiquitin-proteasome system.[72,73]

Accumulation of uraemic toxins may cause or contribute to insulin resistance in patients with ESRD; leptin, IL-6, TNF, indoxyl sulphate and advanced glycation end products are associated with insulin resistance.[74–78] Moreover, the uraemic toxin pseudouridine, which accumulates in the circulation of patients with renal failure, has been reported to impair insulin-mediated glucose utilization in muscle.[79] Patients with ESRD show increased serum levels of the gluconeogenic hormones glucagon and parathyroid hormone as well as resistance to the anabolic hormones insulin, growth hormone and insulin-like growth factor-1.[72] Vitamin D deficiency, obesity, metabolic acidaemia and inflammation also contribute to insulin resistance in advanced CKD.

Poor physical fitness might also contribute to insulin resistance in patients with ESRD.[80] Improvements in tissue oxygen supply and exercise tolerance have been shown to normalize hyperglycaemia and glucose intolerance in patients with erythropoietin-corrected anaemia.[81–83] Treatment with intravenous 1,25-dihydroxyvitamin D_3 and correction of metabolic acidosis also restores insulin resistance in patients on dialysis.[68] Insulin resistance and glucose intolerance may be caused by malnutrition or protein–energy wasting (PEW). Both malnutrition and chronic inflammation have been reported in patients on maintenance haemodialysis.[84–87] Moreover a link between inflammation, malnutrition and atherosclerosis has enabled the identification of malnutrition–inflammation complex syndrome (MICS), which is associated with poor outcomes.[88] Increased insulin resistance and hyperinsulinaemia might cause accelerated atherosclerosis in patients with uraemia and could potentially contribute to the pathogenesis of

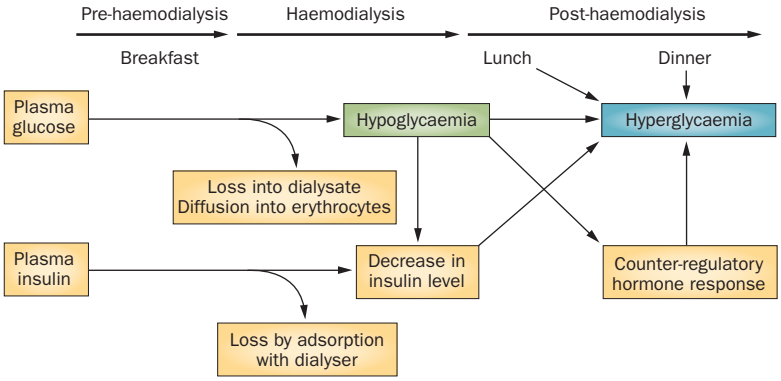

Figure 3 | Mechanisms of haemodialysis-induced hypoglycaemia and haemodialysis-associated hyperglycaemia in patients with diabetes. During haemodialysis, plasma glucose diffuses across the concentration gradient from the blood to the dialysate. In addition, the plasma glucose level at the postdialyser site decreases to less than the glucose concentration of the dialysate, possibly as a result of diffusion of plasma glucose into erythrocytes. Use of glucose-free dialysate is, therefore, associated with an increased likelihood of haemodialysis-induced hypoglycaemia. A decrease in endogenous insulin secretion in response to the decrease in plasma glucose level together with adsorption of insulin by the dialyser results in a decrease in plasma insulin level during haemodialysis. Counter-regulatory hormones are secreted in response to the hypoglycaemic state resulting from the haemodialysis session. The combination of a relative and absolute lack of insulin after haemodialysis, the counter-regulatory hormone response and the postprandial state leads to haemodialysis-associated hyperglycaemia.

hypertension.[89] Insulin resistance (measured using the homeostasis model assessment) is also an independent predictor of cardiovascular mortality in patients on haemodialysis.[90] Inflammation is, therefore, a common factor in insulin resistance, MICS and atherosclerosis.

Increased levels of C-reactive protein are often observed in patients receiving haemodialysis and reflect increases in the release of proinflammatory cytokines such as TNF and IL-6. These cytokines promote cardiovascular disease by contributing to endothelial dysfunction, oxidative stress, insulin resistance and stimulation of adhesion molecules.[91–93] Furthermore, adipocytokines such as TNF and leptin can induce insulin resistance.[78] Diabetic patients with MICS receiving haemodialysis show reduced responses to erythropoietin and increased resistance to insulin.[94] These findings may explain the poor outcomes observed in these patients and demonstrate the importance of diagnosis and therapeutic management of MICS. Although insulin resistance leads to hyperglycaemia in patients with T2DM, insulin resistance in dialysis patients with PEW or MICS tends to result in hypoglycaemia.[42]

Anabolic strategies such as treatment with recombinant growth hormone[95,96] and/or androgens[97,98] as well as exercise,[99,100] either alone or in combination with nutritional supplementation, improve protein stores and represent potential additional approaches for the treatment of PEW.[101] Agents that might reduce inflammation in patients on haemodialysis include nutritional antioxidants, long-chain omega-3 fatty acids, cholecalciferol,[102] statins, angiotensin-converting-enzyme inhibitors and peroxisome proliferator-activated receptor-γ agonists. Pentoxifylline[103] and the TNF receptor and IL-1 receptor antagonist etanercept[104,105] also have anti-inflammatory properties. However, no large randomized clinical trials have tested the efficacy of anti-inflammatory therapies as nutritional interventions to reduce mortality and morbidity in diabetic patients on dialysis. Several pharmacologic agents may stimulate appetite, including anabolic agents, megestrol acetate, dronabinol, melatonin and ghrelin.[106] Although most of these agents have not been studied systematically in patients on haemodialysis, small uncontrolled studies have shown that megestrol acetate can stimulate appetite and induce small increases in weight and serum albumin levels in this population.[101] Large-scale prospective studies of these agents are needed.

Moreover, evidence of a link between levels of FGF23 and inflammation in CKD has been reported,[107] suggesting that regulation of FGF23 might prevent inflammation and hence insulin resistance in this setting. As treatments for insulin resistance do not currently exist, the optimal frequency, duration, dose and modality of dialysis treatment as well as the use of biocompatible membranes and ultrapure dialysate should be carefully considered to reduce the risks of PEW and MICS. Moreover, the nutritional status of the patient should be frequently re-evaluated to reduce the risks of inflammation and insulin resistance.

Insulin removal by haemodialysis

Plasma insulin can be removed by diffusion and/or convection mechanisms owing to its small size (molecular weight 6.2 kDa) and protein-binding rate of 1%. As such, plasma insulin removal could occur due to the concentration gradient in haemodialysis. A study that used a cuprophane membrane dialyser as a low-flux membrane reported that some insulin crossed the membrane during haemodialysis,[108] indicating that insulin might be dialyzed in the presence of an especially high gradient. Moreover, we have shown that plasma insulin levels are lower at the post-dialyser site than at the pre-dialyser site and that insulin clearance is dependent on the membrane type.[109,110] Clearance of biologically active immunoreactive insulin from plasma was greatest when a polysulfone membrane was used and lowest with a polyester–polymer alloy.[111] Although the removal mechanism (diffusion, convection or adsorption) remains to be elucidated, we found that adsorption largely accounts for clearance of plasma insulin during haemodialysis; this mechanism seems to involve electrostatic interactions between the membranes and insulin as well as hydrophobic interactions.[112]

As the low molecular weight of glucose enables it to rapidly transmigrate across the membrane during haemodialysis treatment, the main determinant of plasma glucose levels after a haemodialysis session is the glucose concentration of the dialysate. Changes in plasma insulin levels during haemodialysis, however, are not solely due to insulin removal by the dialyser, but also insulin secretion from pancreatic β-cells. This secretion is determined by dialysis-induced changes in plasma glucose levels and the ability of the β-cells to respond to these changes. In patients who lack endogenous insulin secretion, such as those with insulin-dependent diabetes, the rate of reduction in insulin levels is significantly higher when a polysulphone membrane is used

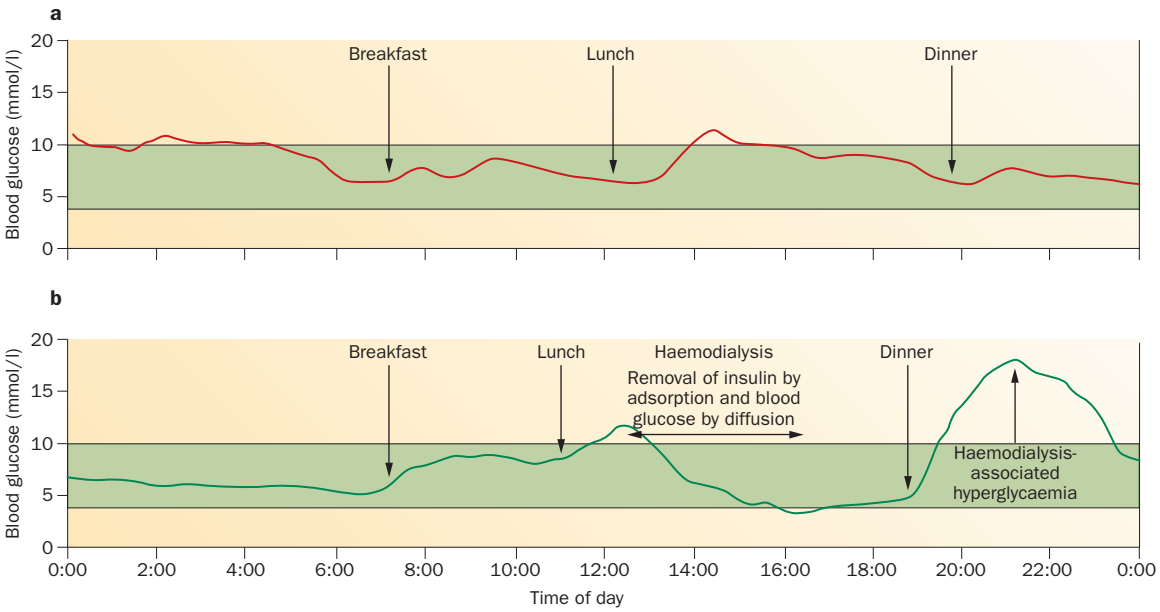

Figure 4 | Haemodialysis-associated hyperglycaemia in a 70-year-old man undergoing continuous glucose monitoring. The patient had been undergoing haemodialysis for 5 years. His haemoglobin A_{1c} and glycated albumin levels were 6.4% and 23.4%, respectively. **a** | A non-haemodialysis day with fairly stable blood glucose levels. **b** | During haemodialysis, the patient's blood glucose level gradually decreased toward the dialysate glucose concentration of 5.55 mmol/l. A further decrease below the dialysate glucose concentration occurred after haemodialysis; the patient was asymptomatic at this time. His plasma cortisol levels increased from 292.43 nmol/l before dialysis to 391.75 nmol/l post-dialysis, whereas his plasma glucagon levels decreased from 156 ng/l before haemodialysis to 106 ng/l after the haemodialysis session. Plasma insulin level was 273.63 pmol/l before haemodialysis and decreased during the session to 70.84 pmol/l after dialysis as a result of adsorption by the dialyser. Pre-haemodialysis, post-haemodialysis and before dinner adrenaline levels were 114.64 pmol/l, 294.79 pmol/l and 141.93 pmol/l, and noradrenaline levels were 1087.62 pmol/l, 2470.80 pmol/l and 1188.11 pmol/l, respectively. Before dinner, the insulin level was 65.28 pmol/l and plasma cortisol was 513.14 nmol/l. The serum glucagon level was increased before dinner (197 ng/l) and the blood glucose level dramatically elevated immediately following the meal. This phenomenon is called haemodialysis-associated hyperglycaemia.

for haemodialysis than when a cellulose triacetate or polyester–polymer alloy membrane is used.[112]

As C-peptide levels reflect endogenous insulin secretion from pancreatic β-cells, plasma insulin removal during haemodialysis is particularly important in diabetic patients with low C-peptide levels, especially those with reduced β-cell function.[110] These patients have an increased risk of hyperglycaemia after haemodialysis treatment, as their β-cells are unable to maintain insulin levels after haemodialysis. High doses of exogenous insulin or antidiabetic agents might be needed to achieve good glycaemic control in these patients because surplus insulin is removed by haemodialysis, particularly if a polysulphone dialyser is used.

Counter-regulatory hormones

The plasma glucose levels of individuals who tend toward a hypoglycaemic state are maintained by lowered insulin secretion and increased secretion of counter-regulatory hormones such as glucagons, adrenocorticotropic hormone and cortisol.[113] Physiological changes in pancreatic α-cells and β-cells, such as a decrease in insulin secretion from β-cells and an increase in glucagon secretion from α-cells, are thought to be induced, and auditory evoked potentials to deteriorate, when blood glucose levels decrease to ≤3.89 mmol/l.[27,114] During haemodialysis, levels of growth hormones decrease and patients show considerably higher than normal glucagon levels.[14,18,108] The lack of reciprocal changes in glucagon levels relative to changes in plasma insulin and glucose concentration suggests impairment of the feedback system, possibly related to the chronic elevation of glucagons.[18,115] A time lag may exist between the decrease in glucose levels and the secretion of counter-regulatory hormones, (Figure 4), the hormones may be lost from the body as a result of dialysis or a failure to secrete the hormones might occur. Capacity for glycogenolysis and gluconeogenesis might also be decreased in patients on haemodialysis.

Changes in blood glucose levels in patients with diabetes owing to the effects of the dialysate occur even after the dialysis session.[10,11,14–16,116] We found that when a 5.55 mmol/l glucose-containing dialysate was used for haemodialysis, the intradialytic decrease in the blood glucose level was greater in insulin-treated patients who had higher pre-dialysis blood glucose levels than in patients not treated with insulin who had lower pre-dialysis blood glucose levels.[16] In diabetic patients with good glycaemic control (that is those with low pre-dialysis blood glucose levels), blood glucose levels tends to decrease, although not significantly, after dialysis sessions. We have observed that in diabetic patients with poor glycaemic control (that is, those with high

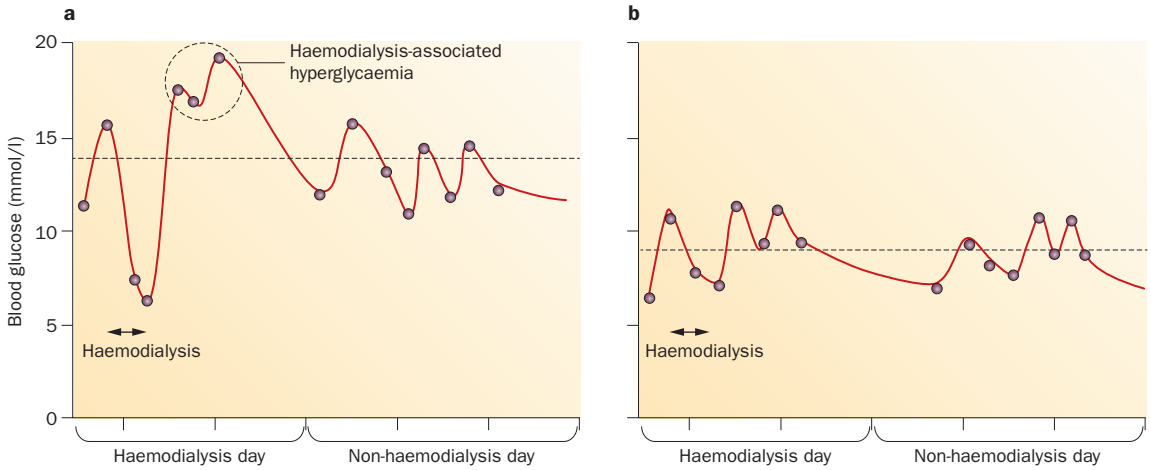

Figure 5 | Daily profiles of plasma glucose levels in diabetic patients on haemodialysis. **a** | Plasma glucose levels in eight patients with poor glycaemic control. **b** | Plasma glucose levels in eight patients with good glycaemic control. The mean plasma glucose level of this group was approximately 4.16 mmol/l higher than that of the good glycaemic control group. Permission obtained from Wiley © Abe, M. *et al*. *Ther. Apher. Dial*. **11**, 288–295 (2007).

pre-dialysis blood glucose levels) blood glucose levels rapidly and markedly decrease during haemodialysis sessions because of the large difference in the glucose levels of the blood and dialysate. Hyperglycaemia can occur after the haemodialysis session, after lunch or in the evening of the day of haemodialysis as a result an absolute or relative deficiency of plasma insulin owing to haemodialysis (Figure 3).[113] Hyperglycaemia in the evening might result from a substantial reduction in plasma insulin levels owing to haemodialysis and stimulation of counter-regulatory hormone secretion in response to the rapid decrease in plasma glucose levels that occurs during haemodialysis. This phenomenon, known as haemodialysis-associated hyperglycaemia (Figure 5), is similar to the Somogyi effect or rebound hyperglycaemia that occurs in response to prolonged hypoglycaemia.

Importantly, haemodialysis-induced hypoglycaemia occurs during or immediately after haemodialysis, whereas haemodialysis-associated hyperglycaemia often occurs late in the evening after the treatment has been completed. As hyperglycaemia may be hidden, both continuous glucose monitoring and self-monitoring of blood glucose on the day of haemodialysis may be useful to detect haemodialysis-induced hypoglycaemia, and haemodialysis-associated hyperglycaemia, respectively.

In general, blood glucose levels in diabetic patients with good glycaemic control do not decrease during dialysis, so these patients do not usually develop hyperglycaemia after dialysis. Therefore, to maintain good glycaemic control in diabetic patients on haemodialysis, hypoglycaemia during the treatment session should be avoided using a glucose-containing dialysate, which prevents the secretion of counter-regulatory hormones, and by decreasing pre-dialysis blood glucose levels so as to minimize fluctuation during haemodialysis (Box 2). We have found that plasma insulin levels are higher in patients with poor glycaemic control than in those with good control,[113] indicating that the former group has more prominent insulin resistance. In this group, administration of an additional insulin injection after haemodialysis seemed to be useful (in the absence of hypoglycaemia or tendency for hypoglycaemia) because of the absolute or relative deficiency of plasma insulin in the circulation and the insulin-resistant status of the patients.

Glycaemic control indices and targets

Haemoglobin A_{1c}

HbA_{1c} level has long been used as an indicator of glycaemic control in clinical practice and in studies of patients with diabetes on dialysis.[6–8,117–123] A US study that included 23,618 diabetic patients on haemodialysis showed that HbA_{1c} levels were associated with mortality.[7] Patients with HbA_{1c} levels >10% had significantly higher adjusted risks of all-cause (hazard ratio [HR] 1.41) and cardiovascular mortality (HR 1.73) than those with HbA_{1c} levels of 5–6%. A German study that investigated the impact of glycaemic control on cardiac and vascular outcomes in 1,255 diabetic patients on haemodialysis showed that those with HbA_{1c} levels of 6–8% or >8% had a higher risk of sudden death during 4 years of follow-up than those with HbA_{1c} levels <6%.[124] By contrast, the risks of myocardial infarction and all-cause mortality did not differ between the groups.

The US Dialysis Outcomes and Practice Pattern Study showed a U-shaped association between HbA_{1c} levels and mortality risk in 9,201 diabetic patients receiving haemodialysis; HbA_{1c} levels <6% and ≥9% were associated with increased risk of death.[125] Similarly, a cohort study with 6 years of follow-up reported that HbA_{1c} levels <6% and >8% were associated with increased mortality in diabetic patients on haemodialysis,[8] whereas a large database analysis showed that extremes of glycaemia (HbA_{1c} levels <6.5% and >11%) were associated with increased risk of death in diabetic patients on chronic haemodialysis.[126] A 2014 meta-analysis also reported that not only high levels of HbA_{1c} (≥8.5%) but also very low HbA_{1c} levels (≤5.4%) were associated with an increased risk of death.[119] Together, these data suggest that not only high HbA_{1c} levels, but also low HbA_{1c} levels related to

Box 2 | Glycaemic control of diabetic patients on haemodialysis

Dialysate
- Use of glucose-free dialysate increases the risk of hypoglycaemia so should be avoided
- Hypoglycaemia might occur during haemodialysis treatment with 5.55 mmol/l glucose-containing dialysate
- No clear consensus exists on the use of hyperglycaemic dialysate (11.1 mmol/l glucose)

Antidiabetic medications
- Metformin is contraindicated
- Caution should be exercised when using sulphonylureas and meglitinide
- Insulin dose reduction may be required due to reduced renal insulin clearance

Insulin resistance
- Insulin resistance accompanied by PEW or MICS can lead to hypoglycaemia
- Evaluation of nutritional status is important to prevent PEW and MICS
- Optimal frequency, duration and dose of dialysis should be carefully considered to reduce the risks of PEW and MICS

Haemodialysis-induced hyperglycaemia
- Self-monitoring of blood glucose levels may help to detect hidden hyperglycaemia after haemodialysis treatment
- Removal of plasma insulin by the dialyser can lead to hyperglycaemia in diabetic patients with reduced β-cell function
- The occurrence of hypoglycaemia during haemodialysis induces secretion of counter-regulatory hormones, which can lead to hyperglycaemia after the treatment session
- Blood glucose levels should be decreased to <11.1 mmol/l before haemodialysis to minimize fluctuations during the treatment session

Assessment of glycaemic control
- Both low and high HbA_{1c} levels are associated with increased mortality in patients with end-stage renal disease
- HbA_{1c} levels may not reflect precise glycaemic control in patients on dialysis
- Glycated albumin may more accurately reflect glycaemic control than HbA_{1c} levels in patients on haemodialysis

Abbreviations: HbA_{1c}, haemoglobin A_{1c}; MICS, malnutrition–inflammation complex syndrome; PEW, protein–energy wasting.

malnutrition or anaemia are associated with increased mortality in patients on haemodialysis. Good glycaemic control targeting a moderate HbA_{1c} range together with avoidance of malnutrition, anaemia and hypoglycaemia may, therefore, improve survival in patients on haemodialysis. KDOQI and Kidney Disease: Improving Global Outcomes clinical practice guidelines recommend that the HbA_{1c} target should be increased to >7% in patients with comorbidities and/or limited life expectancy, and in those at risk of hypoglycaemia, including patients with advanced CKD and those receiving dialysis.[127]

Glycated albumin

The lifespan of red blood cells is decreased from ~120 days to ~60 days in patients on dialysis and blood loss and haemorrhage may occur during the treatment session. In addition, anaemia and erythropoiesis-stimulating agents can increase the proportion of young erythrocytes in the blood leading to a decrease in HbA_{1c} levels, which can lead to a diagnosis of hyperglycaemia being missed. Patients on dialysis, therefore, tend to have low HbA_{1c} levels, which may result in underestimation of glycaemic control. This phenomenon may a mechanism of 'burnt-out diabetes', as described earlier. By contrast, levels of glycated albumin are not significantly associated with the lifespan of red blood cells, haemoglobin levels, or dose of erythropoiesis-stimulating agent in diabetic patients undergoing haemodialysis.[128–130] Levels of glycated albumin might, therefore, be a better indicator of glycaemic control than levels of HbA_{1c} in these patients. Several studies have shown positive associations between levels of glycated albumin and all-cause or cardiovascular mortality in diabetic patients on haemodialysis.[130–135] Notably, no significant associations between average HbA_{1c} levels and mortality were reported.

The management of diabetic patients on haemodialysis 2012 proposed by the Japanese Society for Dialysis Therapy, recommends glycated albumin levels <20% as a target for glycaemic control in patients without a history of cardiovascular events. For those with a history of cardiovascular events and hypoglycaemic episodes, glycated albumin levels <24% are recommended.[136] It is important to note, however, that data on the frequency of measurement of glycated albumin levels are not widely available and outcome studies in patients on dialysis are limited.[137] An American Diabetes Association consensus conference reported that glycated albumin is less affected by low GFR, anaemia or other confounding conditions than are HbA_{1c} and other glycaemic biomarkers,[52] and concluded that glycated albumin levels are, therefore, superior to HbA_{1c} levels with regard to monitoring glycaemic control in patients with CKD and ESRD on haemodialysis. European treatment guidelines for diabetic patients on dialysis do not discuss glycated albumin levels. As current recommendations for the treatment of diabetes in dialysis patients are based on long-term studies of HbA_{1c} levels, further clinical studies are needed to evaluate the efficacy of targeting glycated albumin levels in this population.

Conclusions

In diabetic patients undergoing maintenance haemodialysis, glycaemic control correlates closely with morbidity and mortality. Extremely high and low glycaemic levels are associated with increased morbidity and mortality owing to vascular and diabetic complications as well as malnutrition. In patients with ESRD and particularly those with diabetes, glycaemic status should be closely monitored by frequent, careful measurement of glucose levels, particularly during and after each haemodialysis session. The prevention of haemodialysis-induced hypoglycaemia and the management of haemodialysis-associated hyperglycaemia are particularly important to reduce morbidity and mortality in this population.

Review criteria

We searched MEDLINE and PubMed for original articles and reviews focusing on haemodialysis-induced hypoglycaemia and hyperglycaemia that were published between January 1970 and January 2014. The search terms used were "antidiabetic agent", "diabetes mellitus", "end-stage renal disease", "gluconeogenesis", "glucose concentration in dialysate", "haemodialysis", "hypoglycaemia", "hyperglycaemia", "insulin" and "insulin resistance". All papers identified were full-text papers written in English. We also searched the reference sections of the papers identified for relevant articles.

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Acknowledgements

K.K.Z.'s work is supported by research grants from the NIH/NIDDK (K24-DK091419 and R01-DK078106) and philanthropic grants from Harold Simmons, Louis Chang, and AVEO. The authors appreciate invaluable advice on this manuscript given by K. Kaizu (Abe Clinic and Nihon University School of Medicine, Japan).

Author contributions

M.A. researched the data for the article. Both authors contributed substantially to discussions of the content, wrote the article and reviewed and edited the manuscript before submission.

ERRATUM

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Nat. Rev. Nephrol. advance online publication 7 April 2015; doi:10.1038/nrneph.2015.38

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