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Updates on the Management of Diabetes in Dialysis Patients

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Abstract

Diabetes mellitus is the leading cause of end-stage renal disease (ESRD) in the U.S. and many countries globally. The role of improved glycemic control in ameliorating the exceedingly high mortality risk of diabetic dialysis patients is unclear. The treatment of diabetes in ESRD patients is challenging, given changes in glucose homeostasis, the unclear accuracy of glycemic control metrics, and the altered pharmacokinetics of glucose-lowering drugs by kidney dysfunction, the uremic milieu, and dialysis therapy. Up to one-third of diabetic dialysis patients may experience spontaneous resolution of hyperglycemia with hemoglobin A1c (HbA1c) levels <6%, a phenomenon known as "Burnt-Out Diabetes," which remains with unclear biologic plausibility and undetermined clinical implications. Conventional methods of glycemic control assessment are confounded by the laboratory abnormalities and comorbidities associated with ESRD. Similar to more recent approaches in the general population, there is concern that glucose normalization may be harmful in ESRD patients. There is uncertainty surrounding the optimal glycemic target in this population, although recent epidemiologic data suggest that HbA1c ranges of 6% to 8%, as well as 7 to 9%, are associated with increased survival rates among diabetic dialysis patients. Lastly, many glucose-lowering drugs and their active metabolites are renally metabolized and excreted, and hence, require dose adjustment or avoidance in dialysis patients.

Diabetes mellitus is the leading cause of chronic kidney disease (CKD) in the U.S., accounting for approximately 44% and 38% of incident and prevalent cases of end-stage renal disease (ESRD), respectively.[1] While the total number of new patients with ESRD due to diabetes continues to rise (i.e., 49,603 new cases in 2011), there has been a plateau in the incidence rate over the past decade (i.e., 159 new cases per million in 2011). Over the past

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decade, the mortality rates for diabetic dialysis patients have also declined (i.e., 90 vs. 71 deaths per 1000 patient-years of at-risk time in 2000 vs. 2011, respectively). However, diabetic dialysis patients continue to have poor survival (i.e., 34% over 5 years), worse than those with ESRD due to hypertension and glomerular disease. Thus, there is a compelling need to determine if improved glycemic control with well-managed diabetic pharmacotherapies may ameliorate this exceedingly high mortality risk, or even perhaps be associated with adverse outcomes. In this review, we will discuss: 1) alterations in glucose homeostasis conferred by the uremic milieu; 2) the strengths and limitations of diagnostic tools used to evaluate intermediate- and long-term glycemic control in dialysis patients; 3) existing literature on glycemic targets and outcomes in the dialysis population; and 4) the safety and effectiveness of various diabetic pharmacotherapy regimens in diabetic dialysis patients.

Effects of Kidney Dysfunction and Dialysis on Glucose Homeostasis

Maintenance dialysis patients, with or without diabetes, may experience both hyper- and hypoglycemia through multifactorial mechanisms relating to kidney dysfunction, the uremic environment, and dialysis.[2–5]

Hyperglycemia

In CKD patients without overt diabetes, including those on dialysis, hyperglycemia and impaired glucose tolerance may ensue as a result of increased insulin resistance and decreased insulin secretion.[3,4,6] The pathogenesis and exact site of insulin resistance in dialysis patients has not been fully elucidated[4]; however, uremic toxins are thought to be contributory, as insulin sensitivity improves with dialysis.[7–10] Secondary hyperparathyroidism and vitamin D deficiency may impair insulin secretion, and vitamin D repletion has been shown to improve insulin secretion independent of its effects on parathyroid hormone levels.[4,11,12] While limited data suggest that peritoneal dialysis (PD) confers improved insulin sensitivity compared to hemodialysis,[13] PD may result in significantly greater dialysate glucose exposure, particularly if higher glucose dialysate concentrations are required to achieve ultrafiltration goals. For example, dialysis solutions used by PD patients contain glucose concentrations ranging from 1360 to 3860 mg/dL,[14] and the glucose load delivered by PD may confer as much as 10 to 30% of a patient's total caloric intake.[15]

Hypoglycemia and the "Burnt-Out Diabetes" Phenomenon

In diabetic dialysis patients, spontaneous resolution of hyperglycemia and the apparent normalization of glycated hemoglobin (hemoglobin A1c [HbA1c]) levels, independent of treatment, is commonly observed and referred to as "Burnt-Out Diabetes."[2–5] In one study of 23,618 diabetic dialysis patients from a large U.S. dialysis organization, up to one-third were observed to have HbA1c levels <6% (Figure 1).[16] Frequent hypoglycemic episodes may result in the discontinuation of insulin and oral anti-diabetic medications in dialysis patients.[3–5,16]

Multiple factors may contribute to this condition. First, malnutrition, protein-energy wasting, and diabetic gastroparesis are frequently observed complications in dialysis patients, which heighten the risk of hypoglycemia.[2–4,17] Second, the clearance and degradation of exogenous insulin is reduced in kidney dysfunction, which results in prolongation of insulin half-life.[18] Third, there is a decline in the hepatic clearance of insulin in kidney dysfunction, which may improve after initiation of dialysis.[6] Fourth, decreased nephron mass and kidney function also lead to a reduction in renal gluconeogenesis.[19,20] Finally, the accumulation of some uremic toxins, such as guanidino compounds, may act

similar to biguanide agents used for the treatment of type 2 diabetes, thus mitigating or even "curing" diabetes.[21–23] At this time, the biologic plausibility of burnt-out diabetes as a distinct clinical condition is debatable, and its clinical significance remains unclear.

Monitoring of Glycemic Control in Dialysis Patients

Laboratory abnormalities and comorbidities associated with the uremic state may impact the accuracy of various methods used for assessing intermediate- and long-term glycemic control, including glycated hemoglobin (HbA1c), fructoasmine, and glycated albumin (Table 1). Despite these limitations, the Kidney Disease Quality Outcomes Initiative (KDOQI) and Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines recommend routine measurement of long-term glycemic control using HbA1c, in combination with home blood glucose monitoring, as a cornerstone of diabetes management in CKD and ESRD patients.

Glycated Hemoglobin (HbA1c)

HbA1c is formed by a non-enzymatic reaction between glucose and hemoglobin's beta chain.[24] It measures the concentration of circulating glucose over a 120-day exposure period, and it is the index upon which current standard therapeutic targets for glycemic control are based in the general population.[25–27] The glycation rate of hemoglobin is influenced by various factors, including: 1) length of glucose exposure, 2) glucose concentration, 3) hemoglobin level, 4) pH, and 5) temperature.[3] Hence, numerous ESRD-related factors may result in aberrant HbA1c levels (Table 1). Spuriously elevated HbA1c levels may be observed in the context of elevated blood urea nitrogen (BUN) levels and metabolic acidosis.[28,29] Exposure to high urea concentrations promotes formation of carbamylated hemoglobin, which cannot be distinguished from glycated hemoglobin in certain assays (e.g., electric charge-based assays).[4,29] In contrast, boronate-agarose affinity chromatography and thiobarbituric acid methods provide more robust measurement of HbA1c in dialysis patients.[30–32]

Conversely, both spuriously and truly low HbA1c levels may be observed in the context of anemia, blood transfusions, and conditions associated with shortened erythrocyte life span (e.g., hemoglobinopathies, erythrocyte fragility due to uremia, erythrocyte lysis due to the dialysis procedure), which may consequently lead to underestimation of long-term glucose control and undertreatment of hyperglycemia.[3–5] The frequent utilization of erythropoietin-stimulating agents in dialysis patients also falsely lower HbA1c levels by accelerating erythropoiesis and increasing the proportion of young circulating erythrocytes that have limited time for hemoglobin glycosylation.[33] To address these limitations, various equations accounting for hemoglobin and other laboratory covariates have been developed to better characterize the HbA1c and blood glucose relationship in hemodialysis and PD patients.[34,35]

Fructosamine

Fructosamine is a metric of intermediate-term glycemic control (i.e., 7 to 14 days) and is a measure of the ketoamines formed by the nonenzymatic glycation of serum proteins.[36] While fructosamine may be a more accurate glycemic control metric in anemic dialysis patients, it may also be confounded by a number of conditions, particularly dysproteinemias (Table 1).[3,4] Hence, falsely low fructosamine levels may be observed in PD patients with protein losses in the peritoneal dialysate and in patients with hypoalbuminemia due to protein-energy wasting. Some, but not all, studies have shown that fructosamine is a more accurate measure of glycemic control than HbA1c. In a prospective study of 100 diabetic hemodialysis patients, fructosamine was observed to be a more potent predictor of hospitalization and infections compared to HbA1c.[37] In a more recent study of 503 incident

hemodialysis patients from the CHOICE cohort, a doubling of fructosamine levels was associated with a two-fold higher risk of all-cause and cardiovascular mortality.[38]

Glycated Albumin

Whereas fructosamine is a measure of all glycated serum proteins, glycated albumin is formed by a non-enzymatic reaction between glucose and albumin.[3,4,39] Glycated albumin measures short-term glucose control (i.e., 7 to 14 days), is robust in anemia and conditions of shortened erythrocyte lifespan, but may be confounded by similar pathologic conditions as fructosamine (Table 1). Several studies comparing the interrelationship between blood glucose, glycated albumin, and HbA1c in diabetic dialysis patients vs. control patients without kidney disease have reported a correlation between blood glucose and glycated albumin levels in these two groups.[40–43] However, for any glucose level, HbA1c was lower in dialysis patients vs. control patients, raising the concern that HbA1c underestimates glycemic levels compared to glycated albumin in uremic states.

Elevated glycated albumin levels have also been associated with adverse cardiovascular surrogates (e.g., increased arterial stiffness, vascular calcification)[3,44,45] and hard outcomes. In a prospective study of 444 diabetic dialysis patients by Freedman et al., glycated albumin was observed to be a more potent predictor of death risk compared to HbA1c and glucose levels.[46] For every 5% increase in glycated albumin level, there was a 14% higher risk of all-cause death, whereas no associations between HbA1c, glucose level, and mortality were observed. These findings stand in contrast to a number of other studies that have observed an incremental increase in mortality risk with higher HbA1c.[14,16,47–58] The discrepant findings in the Freedman et al. study may have been due to lack of cumulative glycemic exposure assessment (i.e., lack of time-dependent or time-averaged exposure analysis); an infrequent number of HbA1c measures compared to glycated albumin; and a sparse number of events resulting in limited power.[42] Nonetheless, this important study has prompted interest in glycated albumin as a novel metric of glycemic control and outcomes in dialysis patients. Further studies are needed prior to the adoption of glycated albumin and fructosamine as routinely-used intermediate-term glycemic control metrics in diabetic dialysis patients.

Glycemic Control and Outcomes

In the general population, the landmark Diabetes Control and Complications Trial (DCCT) and the follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) studies demonstrated that intensive vs. standard glycemic control reduces microvascular complications and cardiovascular disease, respectively, in type 1 diabetic patients.[59,60] In the United Kingdom Prospective Diabetes Study (UKPDS), intensive treatment was observed to reduce microvascular complications among type 2 diabetic patients[61,62]; in the 10-year post-trial follow-up study, a reduction in myocardial infarction and all-cause death was also observed in the intensive treatment group despite an attenuation in glycemic differences between the intensive and standard treatment groups over time.[63]

More recently, three randomized controlled trials - ADVANCE, ACCORD, and Veterans Affairs Diabetes Trial (VADT) – sought to examine the impact of tight glycemic control on macrovascular outcomes in type 2 diabetic patients.[64–66] Neither ADVANCE nor VADT showed an improvement in cardiovascular outcomes, while ACCORD, which consisted of patients with underlying cardiovascular disease, reported that intensive treatment was associated with higher cardiovascular mortality risk. There are several explanations for these discrepant findings between the earlier DCCT/EDIC and UKPDS studies and the more recent ADVANCE, ACCORD, and VADT trials, which include: 1) lower cardiovascular risk profiles among the DCCT/EDIC and UKPDS cohorts; 2) comparatively less intensive

glycemic control in the DCCT/EDIC and UKPDS studies (i.e., in the earlier UKPDS study, intensive glycemic control was analogous to conventional glycemic control in the ADVANCE, ACCORD, and VADT trials); and 3) longer follow-up with which to observe hard outcomes in the DCCT/EDIC and UKPDS studies.[67]

These recent data have prompted concern that attempts to normalize glycemic control in populations with high underlying cardiovascular risk may be harmful. This has contributed to the uncertainty surrounding the optimal glycemic target in dialysis patients, in whom there are higher risks of cardiovascular morbidity and mortality. A number of observational studies examining the association between degree of glycemic control and mortality in dialysis patients have shown mixed findings (Table 2). From 1993 to 2006, several studies of small cohort size (<250 patients/study) largely observed that higher HbA1c levels were associated with increased mortality in hemodialysis and PD patients.[47,50,51,56,58]

In a study of 24,875 Fresenius Medical Care diabetic hemodialysis patients by Williams et al., there was no association between HbA1c level and mortality after 1 year.[68] However, these data were limited by its short-term follow-up; lack of repeated HbA1c measures and time-dependent survival models; and residual confounding by malnutrition, inflammation, anemia, and comorbidities.

In a subsequent study of 23,618 DaVita Inc. diabetic hemodialysis patients followed for up to 3 years by Kalantar-Zadeh et al., lower time-varying HbA1c levels were initially associated with increased mortality in unadjusted analyses.[16] However, in subsequent analyses that adjusted for case-mix and malnutrition-inflammation markers and hemoglobin level, higher time-varying HbA1c levels were incrementally associated with higher mortality risk. Using an analogous design with time-varying HbA1c levels, comprehensive adjustment for confounders, and more extended follow-up (i.e., up to three years) Williams et al. then showed that extremes of glycemia (HbA1c<6.5% and >11%) were associated with increased death risk in the Fresenius hemodialysis cohort.[55]

More recently, data from 9201 hemodialysis patients from the U.S. Dialysis Outcomes and Practice Pattern Study (DOPPS) cohort showed a U-shaped association between HbA1c levels and death risk (i.e., HbA1c <6% and   9% were each associated with increased mortality risk).[52] These findings were corroborated by an even larger study by Ricks et al. of 54,757 DaVita hemodialysis patients among whom HbA1c levels <6% and >8% were associated with increased mortality (Figure 2).[53] Despite extensive adjustment for confounders, lower HbA1c may have been a marker of illness and/or malnutrition in these latter observational studies.

Hence, these data might suggest that targeting a moderate HbA1c range is associated with greater survival in dialysis patients with lower comorbidity burden and favorable nutritional status, whereas targeting lower HbA1c levels may exacerbate mortality risk in dialysis patients with underlying illness and malnutrition.

At this time, KDOQI and KDIGO clinical practice guidelines recommend that the HbA1c target should be raised to >7% in patients with comorbidities, limited life expectancy, and those at risk for hypoglycemia, the latter of which include patients with advanced CKD, including those receiving dialysis.[69] However, in the opinion of some of the coauthors of this review,[70] the most reasonable target range for diabetic dialysis patients should be limited to 6 to 8% or 7% to 9%, given higher mortality risks observed with HbA1c<6% and the potential implications of burnt-out diabetes and the high death risk associated with hypoglycemia in these patients.[53,70] Large clinical trials are needed to determine whether intensive vs. moderate vs. liberal glycemic control optimizes morbidity and mortality in dialysis patients.

Treatment of Diabetes in the Dialysis Population

Insulin

Whereas endogenously secreted insulin is degraded by the liver, exogenous insulin is primarily excreted by the kidneys.[18] After being freely filtered by the glomerulus, insulin is reabsorbed principally by the proximal tubule and to a lesser degree by peritubular endothelial cells, where it is degraded into peptide fragments. While there are no absolute guidelines regarding dose adjustments for insulin based on estimated glomerular filtration rate (eGFR), experts recommend an insulin dose reduction of 50% when eGFR is <10ml/ min/1.73m[2.18,71] Upon initiation of dialysis, peripheral insulin resistance may improve, further reducing insulin requirements.[7–9]

PD patients have the option of insulin administration via a subcutaneous (SC) or intraperitoneal (IP) route. IP insulin administration stimulates endogenous insulin secretion and inhibits hepatic gluconeogenesis and ketogenesis,[72] but may also necessitate higher insulin doses due to losses into the dialysate and adsorption to the plastic surface of dialysis solution delivery systems.[73] In a meta-analysis of three trials in diabetic PD patients, IP vs. SC insulin administration was associated with two-fold higher insulin requirements and a greater degree of optimal glycemic control.[74] However, IP insulin regimens may also carry the risk of 1) bacterial contamination during their injection into dialysate bags,[75] 2) peritoneal fibroblastic proliferation,[76] and 3) hepatic subcapsular steatonecrosis.[77] Further study of the safety and effectiveness of long-term IP vs. SC insulin regimens in PD patients is needed.

Oral Agents

The armamentarium of therapeutic agents used for the treatment of diabetes has expanded over the past decade (Table 3). However, the pharmaocokinetic properties of many of these drugs are altered in kidney dysfunction and may thus require dose adjustment or avoidance in dialysis patients.[18,78]

Sulfonylureas (SUs) stimulate insulin secretion by binding to a receptor on the pancreatic beta cells that is a component of the ATP-dependent potassium channel.[18] The older first generation SUs (e.g., acetohexamide, chlorpropamide, tolazamide, tolbutamide) are rarely used and should not be used in dialysis patients, given their long half-life and risk of hypoglycemia among this population. Among the newer, second generation SUs, short-acting glipizide is the preferred agent in dialysis patients, as it is largely metabolized by the liver, has inactive or weakly active metabolites that are excreted in the urine, and has a lower risk of hypoglycemia compared to other SUs (e.g., glyburide, glimepiride).[18,78] Most clinicians, however, avoid the use of SUs in the elderly and in dialysis patients, due to the hypoglycemia risk.

Meglitinides include repaglinide and nateglinide, which are structurally different that SUs but similarly stimulate insulin secretion by regulating ATP-dependent potassium channels on pancreatic beta cells.[79] Repaglinide is the preferred agent in dialysis patients, as it is completely metabolized by the liver, has inactive or weakly active metabolites that are excreted in the urine, and has lower risk of hypoglycemia compared with other agents.[18,78] Nateglinide, while also hepatically metabolized, has renally-excreted active metabolites that may result in hypoglycemia in dialysis patients.

Biguanides consist of metformin, phenformin, and buformin which inhibit hepatic gluconeogenesis, decrease intestinal glucose absorption, and improve peripheral insulin sensitivity.[80] Phenformin was removed from the U.S. market due to its high frequency of severe lactic acidosis, but it is still available in other countries; buformin is also only

available outside of the U.S. Ninety-percent of metformin is renally excreted,[81] and accumulation in kidney dysfunction causes type B (nonhypoxic) lactic acidosis due to 1) enhanced conversion of glucose to lactate in the small intestine, and 2) inhibition of hepatic gluconeogenesis by lactate, pyruvate, and alanine.[82,83] The mortality rate of metformin-associated lactic acidosis is as high as 50%. Hence, U.S. FDA guidelines advise against metformin use when the creatinine in men and women is 1.5mg/dL and 1.4 mg/dL, respectively.[18] While some experts have recommended metformin dose reduction (i.e., 50% reduction, or half of maximal dose) when the eGFR is 30–45ml/min/1.73m^2,[84] the most recent KDIGO guidelines recommend that metformin use should be reevaluated at this range of eGFR, and discontinued when eGFR is <30ml/min/1.73m^2 and hence should not be used in dialysis patients.[69]

Thiazolidinediones (*TZDs*) bind to the peroxisome proliferator-activated receptor-gamma (PPAR-γ) receptor and improves peripheral insulin sensitivity and suppresses hepatic gluconeogenesis.[18] TZDs are wholly metabolized in the liver, and neither the parent drug nor its major metabolites are renally excreted. TZDs may promote edema and congestive heart failure via PPAR-γ-mediated stimulation of distal tubular sodium channels and sodium reabsorption, but this risk may be irrelevant in oliguric and anuric dialysis patients.[85–87] TZDs may also decrease bone formation and increase bone loss and fracture risk, which may bear consequence in patients with underlying CKD-mineral bone disease.[88] However, TZDs may also favorably impact health by improving lipid (e.g., triglyceride, HDL) and adiponectin levels; reducing visceral adiposity; decreasing inflammation; and reducing muscle catabolism and protein-energy wasting.[89–91]

In the general population, observational data and meta-analyses suggest that TZD safety and effectiveness may be dependent on the specific agent used. Whereas studies of rosiglitazone have shown an increased risk of cardiovascular events,[92] studies of pioglitazone have demonstrated a reduced risk of cardiovascular morbidity and mortality.[93]

To date, two rigorous studies examining TZDs and mortality in the dialysis population have shown mixed findings. In a study of 5290 incident dialysis patients with diabetes from the ArMORR cohort, Brunelli et al. showed that TZD use was associated with lower all-cause mortality among insulin-free patients, but not in those who were insulin-requiring.[89] This was irrespective of the type of TZD agent used, and findings were robust in a number of sensitivity analyses that accounted for confounding by indication, severity of disease, reverse causation, and time-varying exposure status. On the basis of these data, it was posited that the benefits of TZDs on peripheral insulin sensitivity may be annulled among those exposed to exogenous insulin. In contrast, Ramirez et al. showed that rosiglitazone use was associated with increased all-cause and cardiovascular mortality among 2393 diabetic hemodialysis patients from the U.S. DOPPS cohort, irrespective of insulin use.[87] However, similar associations were not observed among those who received pioglitazone, and emerging data suggest that pioglitazone is associated with improved survival in dialysis patients.[94]

Dipeptidyl Peptidase-4 Inhibitors (DPP-4 inhibitors) are incretin system compounds and include linagliptin, sitagliptin, and saxagliptin;[18,78] several additional agents in this class have been approved in recent years or are in development. DPP-4 is an enzyme expressed on the surface of various types of cells and deactivates glucagon-like peptide-1 (GLP-1), an incretin hormone which stimulates glucose-dependent insulin secretion. By increasing GLP-1 availability, DPP-4 inhibitors promote insulin release and reduce postprandial glucose levels. Linagliptin is minimally excreted in the urine, but it has not been well studied in the dialysis population. Sitagliptin is largely excreted in the urine, and the recommended dose in dialysis patients is 25 mg orally per day. Saxagliptin and its primary

active metabolite are cleared by hemodialysis and thus should be administered using a reduced dose (2.5 mg orally once a day) after dialysis.

Exenatide and liraglutide are *GLP-1 analogues* that not only facilitate insulin secretion, but also decrease glucagon secretion, delay gastric empying, and promote early satiety and weight loss.[18] Exenatide is an injectable, renally-excreted drug and not recommended in patients with an eGFR<30/ml/min/1.73m^2. Although liraglutide is not metabolized or eliminated by the kidney, there are few data of its use in dialysis patients, and manufacturers caution against administration in mild to severe kidney dysfunction.[69]

Pramlintide is an *analogue of amylin*, a pancreatic beta cell hormone that delays gastric emptying, increases satiety, and suppresses postprandial rises in glucagon levels.[78] It is co-secreted with insulin, primarily renally metabolized and excreted, and has not been studied in dialysis patients.

Alpha-glucosidase inhibitors function by delaying gastrointestinal glucose absorption and reducing postprandial blood glucose peaks.[18,69,78] Gastrointestinal side effects (e.g., abdominal pain, diarrhea, flatulence) has rendered its use infrequent in the general diabetic population. While <2% of acarbose and its active metabolites are renally excreted, its use in dialysis patients is not recommended given inadequate study in this population. Miglitol is renally excreted, and administration is also not advised in patients with kidney dysfunction.

The *sodium-glucose cotransporter 2 (SGLT2) inhibitors* include canagliflozin and dapagliflozin and are a new line of diabetic medications that modestly lower elevated blood glucose and HbA1c levels by inhibiting reabsorption of the filtered glucose load and hence promote the renal excretion of glucose.[95] In animal studies, SGL2 inhibitors have also been shown to reduce albuminuria.[96] At this time, there is a lack of long-term safety and effectiveness data supporting their use in the general type 2 diabetic population, and their use is contraindicated in dialysis patients.

Conclusion

There have been substantial advances in our understanding of the unique glycemic milieu, limitations of contemporary glucose-monitoring methods, and the complex pharmacokinetics of glucose-lowering therapeutic agents in dialysis patients. However, many unanswered questions remain: What is the target range of glycemic control in diabetic dialysis patients? Is diabetes management in diabetic dialysis patients as important as it is in diabetics without advanced CKD, and what is the relative relevance of optimizing hyperglycemia in the context of other diabetic comorbidities among dialysis patients? Does burnt-out diabetes have clinical significance?

Based on existing observational data, intensive glycemic control does not appear to be associated with improved outcomes in dialysis patients who are prone to hypoglycemia and the burnt-out diabetes phenomenon. However, there remains substantial uncertainty with regards to 1) the optimal method for glycemic monitoring in dialysis patients, 2) the impact of these respective methods on glycemic control and hard outcomes in this population, 3) ideal glycemic targets that confer improved morbidity and mortality, and 4) the comparative safety and effectiveness of various glucose-lowering drugs in dialysis patients.

At this time, the critical next steps in closing these knowledge gaps will be to define 1) an accurate and broadly applicable glycemic metric in CKD, 2) the optimal glycemic target ranges in this population (and whether this differs from the general population), and 3) whether our understanding of the natural course of the burnt-out diabetes phenomenon can be used to ameliorate diabetic complications prior to end-organ damage. Given the high

mortality rate among this population, there is compelling need for further investigation of how to optimally manage diabetes in dialysis patients.

Acknowledgments

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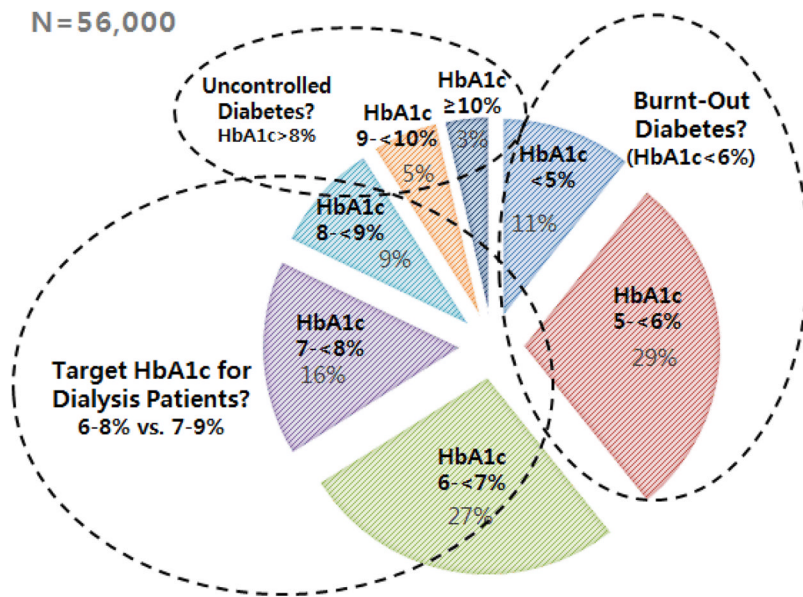
Figure 1.
Approximately one-third of diabetic dialysis patients have an average HbA1c<6%, referred to as "Burnt-Out Diabetes" (data based on Ricks et al., Diabetes 61(30): 708–715, 2012).[53]
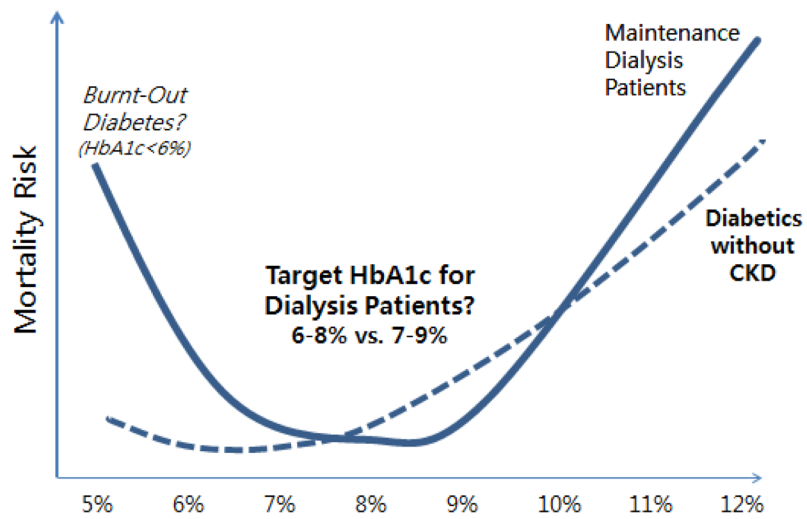
Figure 2.
The optimal target hemoglobin A1c (HbA1c) range for diabetic dialysis patients appears to be different from the general population, e.g. 6% to 8% or 7% to 9% (data based on Ricks et al., Diabetes 61(30): 708–715, 2012).[53]

Table 1

Comparison of Methods of Glycemic Control Assessment

Glycemic Metric	Period of Assessment	Confounders	Strengths	Limitations
Hemoglobin A1c	2–3 months	*Falsely increase:* • Elevated blood urea nitrogen level • Metabolic acidosis *Falsely decrease:* • Anemia • Blood transfusions • Hemoglobinopathies and other disorders of shortened erythrocyte lifespan • Erythropoietin–stimulating agents • Protein-energy wasting	• Routinely available in clinical laboratories • Metric in the general population upon which therapeutic targets are set based on outcomes studies	
Fructosamine	2 weeks	• Altered serum protein states (i.e., peritoneal dialysate protein losses) • Malnutrition • Hepatic disease • Thyroid dysfunction • Pregnancy • Hyperuricemia • Smoking • Steroid use	• Robust in states of altered hemoglobin level and erythropoiesis	• No reference levels • Not routinely available in clinical laboratories • Limited data on outcomes (i.e., microvascular complications)
Glycated Albumin	2 weeks	• Altered serum protein states (i.e., peritoneal dialysate protein losses) • Malnutrition • Hepatic disease • Thyroid dysfunction • Pregnancy • Hyperuricemia • Smoking • Steroid use	• Robust in states of altered hemoglobin level and erythropoiesis	• No reference levels • Not routinely available in clinical laboratories • Limited data on outcomes (i.e., microvascular complications)

Adapted from Kovesdy CP, Sharma K, Kalantar-Zadeh K. AJKD 2008; 52: 766–777.

Table 2

Observational Studies of Glycemic Control and Mortality in Dialysis Patients

Author	Study Cohort (Country)	Period of exposure definition	Results
Tzamaloukas (1993)[47]	226 dialysis (PD and HD) patients with type 1 and 2 DM (USA)	Glycemic control during the 1st six months of study	• Good glycemic control (50% of glucose measurements within acceptable range, or HbA1c 5–10%) associated with lower mortality vs. poor glycemic control (HbA1c <10%) • Study limitations included lack of adjustment for confounders
Wu (1997)[56]	137 HD patients with type 2 DM (Taiwan)	Pre-dialysis glycemic control within six months prior to starting HD	• Good glycemic control (HbA1c 5–10%) associated with lower all-cause mortality vs. poor glycemic control (A1c >10%)
Yu (1997)[58]	60 PD patients with type 2 DM (Taiwan)	Pre-dialysis glycemic control within 6 months before starting HD (measured monthly)	• Good glycemic control (A1c all 5–10%) associated with lower all-cause mortality vs. poor glycemic control (A1c >10% at least once)
Morioka (2001)[50]	150 incident HD patients with type 1 and 2 DM (Japan)	HbA1c before HD initiation	• Higher HbA1c associated with increased mortality
McMurray (2002)[97]	83 dialysis (HD and PD) patients with type 1 and 2 DM (USA)	Nonrandomized interventional trial of intensive education/care vs. control	• Study group with decline in HbA1c from 6.9% to 6.3%; no change in HbA1c in control group • Tight control improved QOL, but no improvement in survival
Oomichi (2006)[51]	114 HD patients with type 1 and 2 DM (Japan)	Mean HbA1c during the 3 month period prior to study entry	• Higher Hb A1c (>8%) associated with increased mortality vs. HbA1c <6.5%
Williams (2006)[68]	24,875 HD patients with type 1 and 2 DM (USA – Fresenius)	Baseline HbA1c during the 3 month period prior to study entry	• No association between HbA1c and survival • Study limitations included short-term follow-up, lack of repeated measured for HbA1c, and residual confounding by malnutrition, inflammation, and anemia
Kalantar-Zadeh (2007)[16]	23,618 HD patients with DM (USA – DaVita)	Time-dependent HbA1c	• Higher HbA1c incrementally associated with increased mortality
Okada (2007)[98]	78 HD patients with type 2 DM (Japan)	Mean HbA1c during 1 year period after HD initiation AND Mean HbA1c over 3 months prior to study entry	• No association between HbA1c and all-cause mortality

Author	Study Cohort (Country)	Period of exposure definition	Results
Ishimura (2009)[49]	122 HD patients with type 1 and 2 DM (Japan)	Mean A1c of 3 values measured during 3 months prior to study entry	• Higher HbA1c associated with increased mortality
Dreschsler (2009)[48]	1255 HD patients with type 2 DM (Germany)	Baseline HbA1c	• HbA1c >8% and >6–8% associated with increased sudden cardiac death and all-cause mortality vs. 6%
Williams (2010)[55]	24,875 HD patients with type 1 and 2 DM (USA – Fresenius)	Time dependent HbA1c	• Time-dependent HbA1c<6.5% and >11% associated with increased mortality risk
Shurraw (2010)[99]	1454 HD patients type 1 and 2 DM (Canada)	Monthly HbA1c averaged over 3 months pre- and post-HD initiation	• No association between HbA1c and mortality risk
Shima (2010)[100]	245 HD patients with type 1 and 2 DM (Japan)	Time averaged HbA1c (measured monthly)	• No association between HbA1c and mortality risk
Duong (2011)[14]	2798 PD patients with DM (USA – DaVita)	Baseline and time-averaged HbA1c	• Time-averaged HbA1c levels >8% incrementally associated with increased mortality risk
Sturm (2011)[54]	78 dialysis (PD and HD) patients with type 1 and 2 DM	Time-varying HbA1c (measured every 3 months)	• Lower HbA1c levels <7% associated with decreased mortality risk
Ricks (2012)[53]	54,757 HD patients with DM (USA – DaVita)	Baseline and time-averaged HbA1c	• Time-averaged HbA1c>8% and <6% associated with increased mortality risk
Ramirez (2012)[52]	9201 HD patients with type 1 and 2 DM (USA DOPPS only)	Mean HbA1c during 1st eight months after study entry	• HbA1c <6% and 9% associated with increased all-cause mortality risk
Yoo (2012)[57]	140 PD patients with DM (Korea)	Averaged monthly or quarterly HbA1c levels during 1st year after PD initiation	• All-cause and CV mortality higher in highest vs. lowest HbA1c tertile
Kim (2013)[101]	347 HD patients with DM (USA)	Baseline HbA1c	• HbA1c <6% associated with increased all-cause mortality risk

Abbreviations: PD, peritoneal dialysis; HD, hemodialysis; DM, diabetes; HbA1c, hemoglobin A1c; QOL, quality of life; DOPPS, Dialysis Outcomes and Practice Patterns Study; CV, cardiovascular

Table 3

Oral Diabetic Agents

Medication Class	Mechanism of action	Medication	Usage in dialysis patients	Side effects
Sulfonylureas	• Bind to receptor on pancreatic beta cell and stimulates insulin release	*1st generation:* Acetohexamide Chlorpropamide Tolazamide Tolbutamide *2nd generation:* Glipizide Gliclazide Glimepiride Glyburide	Avoid use of 1st generation agents in dialysis patients Glipizide is the agent of choice	• Hypoglycemia • Hypersensitivity in patients with sulfa allergies • Nausea • Abnormal liver function tests
Meglitinides	• Stimulate endogenous insulin secretion by regulation of ATP-dependent potassium channels on pancreatic beta cells	Repaglinide Nateglinide	Dose reductions not specified, but no clear guidelines Avoid use in dialysis patients	• Hypoglycemia
Biguanides	• Inhibits hepatic gluconeogenesis • Decrease intestinal glucose absorption • Improve peripheral insulin sensitivity	Metformin	Avoid use in dialysis patients	• Lactic acidosis (incidence 0.03 cases per 1000 patient-years; mortality 50%) • Nausea • Diarrhea • Metallic taste
Thiazolidine-diones	• Improves peripheral insulin sensitivity • Suppresses hepatic gluconeogenesis • May improve beta-cell function	Rosiglitazone (soley PPAR-gamma agonist) Pioglitazone (also has PPAR-alpha effects)	Restricted use by manufacturer Dose adjustment not required	• Hypoglycemia • Weight gain • Fluid retention • Edema • Congestive heart failure (contraindicated in patients with New York Heart Association Class III and IV Congestive Heart Failure) • Abnormal liver function tests • Bone loss, decreased formation, increased fracture risk

Medication Class	Mechanism of action	Medication	Usage in dialysis patients	Side effects
Dipeptidyl Peptidase-4 (DPP-4) Inhibitors	• Promotes insulin release by deactivating the DPP-4 enzyme which is a deactivator of Glucagon-like Peptide-1 (which stimulates insulin secretion)	Sitagliptin Saxagliptin Linagliptin	Dose reduction by 75% Dose reduction to 25 mg po qday, given after dialysis Not well studied in dialysis patients	• Pancreatitis • Abnormal liver function tests • Skin reactions
Glucagon-like Peptide 1 Analogues	• Stimulate glucose-dependent insulin release from pancreatic beta cells • Delays gastric emptying • Inhibits glucagon release • Decreases appetite	Exenatide Liraglutide	Avoid use in dialysis patients Avoid use in dialysis patients	• Nausea • Pancreatitis • Diarrhea
Amylin Analogues	• Stimulate glucose- dependent insulin release from pancreatic beta cells • Delays gastric emptying • Inhibits glucagon release • Decreases appetite	Pramlintide	Avoid use in dialysis patients	• Nausea • Hypoglycemia
Alpha-glucosidase inhibitors	• Inhibit alpha-glucosidases (gastrointestinal enzymes that convert complex polysaccharide carbohydrates into monosaccharides) which inhibit gastrointestinal glucose absorption	Acarbose Miglitol	Avoid use in dialysis patients due to limited study	• Abdominal discomfort • Diarrhea • Flatulence
Sodium-glucose cotransporter 2 inhibitors	• Inhibit proximal tubular reabsorption of filtered glucose and promote renal excretion of glucose • Reduces weight • Reduces blood pressure	Canagliflozin Dapagliflozin	Avoid use in dialysis patients	• Vulvovaginal candidiasis • Genital tract infections • Urinary tract infections