CASE IN POINT

Burnt Out? The Phenomenon of Type 2 Diabetes Mellitus in End-Stage Renal Disease

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In patients with T2DM and ESRD, insulin is the antidiabetic medication of choice with a hemoglobin A_{1c} target of 6 to 8%, using fructosamine levels or other measures for better assessment of glycemic control.

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Fed Pract. 2020;37(11):580-585. doi:10.12788/fp.0076

More than 34 million adults in the US have type 2 diabetes mellitus (T2DM), a chronic progressive disease identified by worsening hyperglycemia and micro- and macrovascular complications.[1] Consequently, 12.2% of the US adult population is currently at risk for macrovascular diseases, such as stroke and coronary artery disease (CAD) and microvascular diseases, such as neuropathy and diabetic nephropathy.[1]

T2DM is the most common comorbid risk factor for chronic kidney disease (CKD) and the leading cause of end-stage renal disease (ESRD). As of 2017, about 750,000 Americans have CKD stage 5 requiring dialysis, and 50% of these patients have preexisting diabetic nephropathy.[2] Rates of mortality and morbidity are observed to be higher in patients with both CKD and T2DM compared with patients with CKD without T2DM.[2] Previous clinical trials, including the United Kingdom Prospective Diabetes Study of 1998, have proven that optimal glycemic control decreases the risk of complications of T2DM (ie, nephropathy) in the general population.[3] Conversely, tight glycemic control that targets hemoglobin A_{1c} (HbA_{1c}) < 7%, in patients with T2DM with ESRD has not shown the same benefits and may lead to worse outcomes. It is postulated that this may be due to the increased incidence of hypoglycemia in this patient population.[4]

Dialysis has varying effects on patients both with and without T2DM. While patients with ESRD without T2DM have the potential to develop impaired glucose tolerance and T2DM, about 33% of patients with T2DM on dialysis actually have HbA_{1c} < 6%.[5] In these patients, glycemic control improves spontaneously as their disease progresses, leading to a decrease or cessation of insulin or other antidiabetic medications. This phenomenon, known as burnt-out diabetes, is characterized by (1) alterations in glucose homeostasis and normoglycemia without antidiabetic treatment; (2) HbA_{1c} levels < 6% despite having established T2DM; (3) decline in insulin requirements or cessation of insulin altogether; and (4) spontaneous hypoglycemia.

There is a misconception that burnt-out diabetes is a favorable condition due to the alteration of the natural course of T2DM. Although this may be true, patients with this condition are prone to develop hypoglycemic episodes and may be linked to poor survival outcomes due to low HbA_{1c}.[6,7]

Since Kalantar-Zadeh and colleagues presented a 2009 case study, there has been a lack of research regarding this unique condition.[8] The purpose of this case study is to shed further light on burnt-out diabetes and present a patient case pertaining to the challenges of glycemic control in ESRD.

CASE PRESENTATION

Mr. A is a 49-year-old Hispanic male veteran with a history of ESRD on hemodialysis (HD) for 6 years, anemia of CKD, and T2DM for 22 years. The patient also has an extensive cardiovascular disease history, including hypertension, hyperlipidemia, and CAD status post-4-vessel coronary artery bypass graft in December 2014. The patient receives in-home HD Monday, Wednesday, and Friday and is on the wait list for kidney transplantation. The patient's T2DM is managed by a primary care clinical pharmacy specialist (CPS) at the Michael E. DeBakey Veteran Affairs

TABLE 1 Patient Self-Monitoring Blood Glucose April 25 to June 5, 2018[a]

Test Times	Before Breakfast (n = 24)	Before Dinner (n = 24)	Bedtime (n = 15)
Average blood glucose, mg/dL	188	241	248

[a]For the patient's blood glucose readings, 41% were < 80 mg/dL, 32.4% were 80-180 mg/dL, and 63.5% were > 180 mg/dL.

Medical Center (MEDVAMC) in Houston, Texas.

Mr. A's antidiabetic regimen is 45 units of subcutaneous insulin glargine every morning; insulin aspart sliding scale (about 15-27 units) subcutaneous 3 times daily with meals; and saxagliptin 2.5 mg by mouth once daily.

At a follow-up visit with the CPS, Mr. A stated, "I feel fine except for the occasional low blood sugar episode." The patient's most recent HbA_{1c} was 6.1%, and he reported medication adherence and no signs or symptoms of hyperglycemia (ie, polydipsia, polyphagia, nocturia, visual disturbances). Mr. A reported no use of alcohol, tobacco, or illicit drugs. He walks 1 mile every other day and participates in self-monitoring blood glucose (SMBG) about 2 to 3 times daily (Table 1).

Although Mr. A's most recent HbA_{1c} was well controlled, his estimated fasting blood glucose at the same laboratory draw was 224 mg/dL. His SMBG readings in the past month also were elevated with higher readings in the evening. Mr. A attributed the elevated readings to dietary excursions and a high carbohydrate intake. At this visit, the CPS increased his insulin glargine dose to 50 units subcutaneous every morning and educated him on lifestyle modifications. Follow-up with the CPS was scheduled for 2 months from the day of the visit.

Analysis

Few articles on potential contributors to burnt-out diabetes have been published.[6,7] These articles discuss decreased renal and hepatic clearance of insulin (which increases its half-life) hypoglycemia during HD, and low HbA_{1c} due to preexisting anemia. Inappropriately low HbA_{1c} levels may be secondary to, but not limited to, hemolysis, recent blood transfusion, acute blood loss, and medications, such as erythropoietin-stimulating agents (ESAs).[9] The conditions that affect red blood cell turnover are common in patients with advanced CKD and may result in discrepancies in HbA_{1c} levels.

Glycated hemoglobin is a series of minor hemoglobin components formed by the adduction of various carbohydrate molecules to hemoglobin. HbA_{1c} is the largest fraction formed and the most consistent index of the concentration of glucose in the blood.[10] Hence, HbA_{1c} is the traditional indicator of overall glycemic control. The current HbA_{1c} goals recommended by the American Diabetes Association are derived from landmark trials conducted with patients in the general adult diabetic non-CKD population. However, hemoglobin measurements can be confounded by conditions present in ESRD and tend to underestimate glucose measurements in patients with T2DM on HD. Despite this, HbA_{1c} is still regarded as a reasonable measure of glycemic control even in patients with ESRD; however, alternative markers of glycemia may be preferable.[11]

Although HbA_{1c} is the gold standard, there are other laboratory measures of average glycemic control available. Fructosamine is a ketoamine formed when glucose binds to serum proteins. When these proteins are exposed to high concentrations of glucose, they experience increased glycation. Fructosamine assays measure the total glycated serum proteins, of which albumin accounts for about 90%.[11] Because the half-life of serum proteins is about 20 days, fructosamine levels can reflect glycemic control over a 2- to 3-week period. This is advantageous in conditions that affect the average age of red blood cells, in pregnancy where frequent monitoring and measures of short-term glucose control are especially important, and in the evaluation of a medication adjustment in the management of T2DM. However, this test is not without its limitations. It is less reliable in settings of decreased protein levels (eg, liver disease), there is a lack of availability in routine practice, and reference levels have not been established.[11]

Fructosamine has been shown to be strongly associated with mean blood

TABLE 2 Association of Glycemic Control Measures[11]

Glucose, mg/dL	Fructosamine, µmol	Hemoglobin A_{1c},%
90	212.5	5.0
120	250.0	6.0
150	287.5	7.0
180	325.0	8.0
210	362.5	9.0
240	400.0	10.0
270	437.5	11.0
300	475.0	12.0
330	512.5	13.0
360	550.0	14.0
390	587.5	15.0

TABLE 3 Patient's Laboratory Results

Tests	September 11, 2018	November 6, 2018
Fructosamine		
Level, µmol/L	361	370
Average glucose mg/dL	210	214
Hemoglobin A_{1c},		
Level, %	7.3	6.9
Average glucose, mg/dL	162.8	151.3
Glucometer		
Date range included	April 25 - June 5	October 16 - November 13
Average glucose, mg/dL	202	250

glucose and HbA_{1c} (Table 2). In 2010, Mittman and colleagues published a study that compared HbA_{1c} with fructosamine and their correlation to glycemic control and morbidity, defined as rates of hospitalization and infection.[12] The study included 100 patients with T2DM on HD with a mean age of 63 years, 54% were women, mean HbA_{1c} of 7.2%, and mean dialysis duration of 3 years. Average follow-up was 3 years. At the end of follow-up, Mittman and colleagues found that HbA_{1c} and fructosamine were highly correlated and associated with serum glucose ($P < .01$). However, fructosamine was found to be more highly correlated with mean glucose levels when those levels were below 150 mg/dL ($P = .01$). A higher fructosamine level, not HbA_{1c} was a more significant predictor of hospitalization ($P = .007$) and infection ($P = .001$). Mittman and colleagues presented evidence for the use of fructosamine over HbA_{1c} in patients with T2DM on HD.[12]

Hypoglycemic Episodes

At the 2-month follow-up visit with the CPS, Mr. A reported having 5 hypoglycemic episodes in the past 30 days. He also stated he would forget to take his insulin aspart dose before dinner about 3 to 4 times a week but would take it 30 to 60 minutes after the meal. Mr. A did not bring his glucometer or SMBG readings to the visit, but he indicated that his blood glucose levels continued to fluctuate and were elevated when consuming carbohydrates.

Laboratory tests 1 month prior to the 2-month follow-up visit showed HbA_{1c} of 7.3%, which had increased from his previous level of 6.1%. He was counseled on the proper administration of insulin aspart and lifestyle modifications. A fructosamine level was ordered at this visit to further assess his glycemic control. A follow-up appointment and laboratory workup (fructosamine and HbA_{1c}) were scheduled for 2 months from the visit (Table 3).

Mr. A was educated on the unreliability of his HbA_{1c} levels secondary to his condition of ESRD on HD. He was counseled on the purpose of fructosamine and how it may be a better predictor of his glycemic control and morbidity. Mr. A continued to be followed closely by the primary care CPS for T2DM management.

DISCUSSION

Management of T2DM in patients with ESRD presents challenges for clinicians in determining HbA_{1c} goals and selecting appropriate medication options. The 2012 Kidney Disease Outcomes Quality Initiative (KDOQI) diabetes guideline does not recommend treatment for patients with substantially reduced kidney function to a target $HbA_{1c} < 7\%$ due to risk of hypoglycemia.[13] Although a target $HbA_{1c} > 7\%$ is suggested for these patients, little is known about appropriate glycemic control in these patients as there is a paucity of prospective, randomized clinical trials that include patients with advanced CKD.[13]

Moreover, many oral antidiabetic

TABLE 4 Common Antidiabetic Agents Used at MEDVAMC[17-24]

Agents	CKD Stages 3-5: eGFR, mL/min/1.73m^2
Sulfonylureas (2nd generation)	
Glipizide	eGFR < 50: 2.5 mg/d (initial) to 20 mg/d (maximum)
Glimepiride	1 mg/d (initial); consider alternative therapy if eGFR < 15
Biguanides	
Metformin	eGFR 30 to 45: do not initiate; eGFR < 30: contraindicated
Thiazolidinediones	
Pioglitazone	No dosage adjustment necessary
α-glucosidase inhibitor	
Acarbose	Creatinine > 2 mg/dL or eGFR < 25: not recommended
DPP-4 inhibitor	
Alogliptin	CrCl ≥ 30 to < 60 mL/min: 12.5 mg daily CrCl ≥ 15 to < 30 mL/min: 6.25 mg daily ESRD: 6.25 mg daily without regard to timing of HD
GLP-1 agonist	
Liraglutide	No dosage adjustment necessary; limited data in ESRD
SGLT-2 inhibitor	
Empagliflozin	eGFR 30-45: do not initiate; eGFR < 30: contraindicated

Abbreviations: CKD, chronic kidney disease; CrCl, creatinine clearance; DPP, dipeptidyl peptidase; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; GLP, glucagon-like peptide; MEDVAMC, Michael E. DeBakey Veteran Affairs Medical Center, Houston, Texas; SGLT, sodium glucose cotransporter.

medications and their metabolites are cleared by the kidneys and, therefore, pose with potential harm for patients with CKD. Because of this, insulin is the medication of choice for patients with ESRD.[7] Although insulin requirements may diminish with worsening kidney function, insulin provides the safest method of glycemic control. Insulin dosing can be individualized according to a patient's renal status as there is no uniformity in renal dose adjustments. There are some noninsulin antidiabetic agents that can be used in ESRD, but use of these agents requires close monitoring and evaluation of the medication's pharmacokinetics (Table 4). Overall, medication management can be a difficult task for patients with T2DM and ESRD, but antidiabetic regimens may be reduced or discontinued altogether in burnt-out diabetes.

One of 3 patients with T2DM and ESRD on dialysis has burnt-out diabetes, defined as a phenomenon in which glucose homeostasis is altered to cause normoglycemia, spontaneous hypoglycemia, and decreased insulin requirements in established patients with T2DM.[5] Although Mr. A had a normal-to-low HbA_{1c}, he did not meet these criteria. Due to his elevated SMBG readings, he did not have normoglycemia and did require an increase in his basal insulin dose. Therefore, our patient did not have burnt-out diabetes.

Mr. A represents the relevant issue of inappropriately and unreliably low HbA_{1c} levels due to various factors in ESRD. Our patient did not receive a blood transfusion in the past 2 years and was not on ESA therapy; nevertheless, Mr. A was a patient with ESRD on HD with a diagnosis of anemia. These diagnoses are confounders for low HbA_{1c} values. When fructosamine levels were drawn for Mr. A on September 11, 2018 and November 6, 2018, they correlated well with his serum glucose and SMBG readings. This indicated to the CPS that the patient's glycemic control was poor despite a promising HbA_{1c} level.

This patient's case and supporting evidence suggests that other measures of glycemic control (eg, fructosamine) can be used to supplement HbA_{1c}, serum glucose, and glucometer readings to provide an accurate assessment of glycemic control in T2DM. Fructosamine also can assist HbA_{1c} with predicting morbidity and potentially mortality, which are of great importance in this patient population.

Kalantar-Zadeh and colleagues conducted a study of 23,618 patients with T2DM on dialysis to observe mortality in association with HbA_{1c}.[5] This analysis showed that patients with HbA_{1c} levels < 5% or > 8% had a higher risk of mortality; higher values of HbA_{1c} (> 10%) were associated with increased death risk vs all other values. In the unadjusted analysis, HbA_{1c} levels between 6 and 8% had the lowest death risk (hazard ratios [HR] 0.8 - 0.9, 95% CI) compared with those of higher and lower HbA_{1c} ranges.[5] In nonanemic patients, HbA_{1c} > 6% was associated with increased death risk, whereas anemic patients did not show this trend.

Other studies made similar observations. In 2001, Morioka and colleagues published an observational study of 150 patients with DM on intermittent hemodialysis. The study analyzed survival and HbA_{1c} levels at 1, 3, and 5 years. The study found that at 1, 3, and 5 years, patients with HbA_{1c} < 7.5% had better survival than did patients with HbA_{1c} > 7.5% (3.6 years vs 2.0 years, P = .008). Morioka and colleagues also found that there was a 13% increase in death per 1% increase in HbA_{1c}.[14] Oomichi and colleagues conducted an observational study of 114 patients with T2DM and ESRD on intermittent hemodialysis. Patients with fair control (HbA_{1c} 6.5 - 8%) and good control (HbA_{1c} < 6.5%) were compared with patients with poor control (HbA_{1c} > 8%); it was found that the poor control group had nearly triple the mortality when compared with the good and fair control groups (HR = 2.89, P = .01).[15] Park and colleagues also saw a similar observation in a study of 1,239 patients with ESRD and DM; 70% of these patients were on intermittent hemodialysis. Patients with poor control (HbA_{1c} ≥ 8%) had worse survival outcomes than those with HbA_{1c} < 8% (HR 2.2, P < .001).[16]

Our patient case forced us to ask the question, "What should our patient's HbA_{1c} goals be?" In the study by Oomichi and colleagues, a HbA_{1c} level of 8% has usefulness as a "signpost for management of glycemic control."[15] All patients' goals should be individualized based on various factors (eg, age, comorbidities), but based on the survival studies above, a HbA_{1c} goal range of 6 to 8% may be optimal.

CONCLUSIONS

Patients with T2DM and ESRD on dialysis may have higher morbidity and mortality rates than the rates of those without T2DM. It has been shown in various studies that very low HbA_{1c} (< 5%) and high HbA_{1c} (> 8%) are associated with poor survival. Some patients with T2DM on dialysis may experience burnt-out diabetes in which they may have normoglycemia and a HbA_{1c} below goal; despite these facts, this condition is not positive and can be linked to bad outcomes. In patients with T2DM and ESRD, insulin is the antidiabetic medication of choice, and we recommend a HbA_{1c} target of 6 to 8%. In this patient population, consider using fructosamine levels or other measures of glycemic control to supplement HbA_{1c} and glucose values to provide a better assessment of glycemic control, morbidity, and mortality. Larger clinical trials are needed to assist in answering questions regarding mortality and optimal HbA_{1c} targets in burnt-out diabetes.

Author disclosures

The authors report no actual or potential conflicts of interest with regard to this article.

References

1. Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2020. https://www.cdc.gov/diabetes/data/statistics-report/index.html. Updated August 28, 2020. Accessed November 17, 2020.
2. Saran R, Robinson B, et al. US renal data system 2019 annual data report: epidemiology of klidney disease in the United States. *Am J Kidney Dis.* 2020 Jan;75(1 suppl 1):A6-A7. doi:10.1053/j.ajkd.2019.09.003. Epub 2019 Nov 5.
3. UK Prospective Diabetes Study Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet.* 1998;352(9131):854-865.
4. Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med.* 2008;358(24):2545-2559. doi:10.1056/NEJMoa0802743
5. Kalantar-Zadeh K, Kopple JD, Regidor DL, et al. A_{1c} and survival in maintenance hemodialysis patients. *Diabetes Care.* 2007;30(5):1049-10.55. doi:10.2337/dc06-2127
6. Park J, Lertdumrongluk P, Molnar MZ, Kovesdy CP, Kalantar-Zadeh K. Glycemic control in diabetic dialysis patients and the burnt-out diabetes phenomenon. *Curr Diab Rep.* 2012;12(4):432-439. doi:10.1007/s11892-012-0286-3
7. Rhee CM, Leung AM, Kovesdy CP, Lynch KE, Brent GA, Kalantar-Zadeh K. Updates on the management of

diabetes in dialysis patients. *Semin Dial*. 2014;27(2):135-145. doi:10.1111/sdi.12198

8. Kalantar-Zadeh K, Derose SF, Nicholas S, Benner D, Sharma K, Kovesdy CP. Burnt-out diabetes: impact of chronic kidney disease progression on the natural course of diabetes mellitus. *J Ren Nutr.* 2009;19(1):33-37. doi:10.1053/j.jrn.2008.11.012
9. Unnikrishnan R, Anjana RM, Mohan V. Drugs affecting HbA_{1c} levels. *Indian J Endocrinol Metab.* 2012;16(4):528-531. doi:10.4103/2230-8210.98004
10. Makris K, Spanou L. Is there a relationship between mean blood glucose and glycated hemoglobin? *J Diabetes Sci Technol.* 2011;5(6):1572-1583. doi:10.1177/193229681100500634
11. Wright LAC, Hirsch IB. The challenge of the use of glycemic biomarkers in diabetes: reflecting on hemoglobin A_{1c}, 1,5-anhydroglucitol, and the glycated proteins fructosamine and glycated albumin. *Diabetes Spectr.* 2012;25(3):141-148. doi:10.2337/diaspect.25.3.141
12. Mittman N, Desiraju B, Fazil I, et al. Serum fructosamine versus glycosylated hemoglobin as an index of glycemic control, hospitalization, and infection in diabetic hemodialysis patients. *Kidney Int.* 2010;78 (suppl 117):S41-S45. doi:10.1038/ki.2010.193
13. National Kidney Foundation. KDOQI clinical practice guideline for diabetes and CKD: 2012 update. *Am J Kidney Dis.* 2012;60(5):850-886. doi:10.1053/j.ajkd.2012.07.005
14. Morioka T, Emoto M, Tabata T, et al. Glycemic control is a predictor of survival for diabetic patients on hemodialysis. *Diabetes Care*. 2001;24(5):909-913. doi.10.2337/diacare.24.5.909
15. Oomichi T, Emoto M, Tabata T, et al. Impact of glycemic control on survival of diabetic patients on chronic regular hemodialysis: a 7-year observational study. *Diabetes Care*. 2006;29(7):1496-1500. doi:10.2337/dc05-1887
16. Park JI, Bae E, Kim YL, et al. Glycemic control and mortality in diabetic patients undergoing dialysis focusing on the effects of age and dialysis type: a prospective cohort study in Korea. *PLoS ONE.* 2015;10(8):e0136085. doi:10.1371/journal.pone.0136085
17. Glucotrol tablets [package insert]. New York, NY: Pfizer; October 2016.
18. Amaryl [package insert]. Bridgewater, NJ: Sanofi-Aventis; December 2018.
19. Glucophage [package insert]. Princeton, NJ: Bristol-Myers Squibb; May 2018.
20. Actos [package insert]. Deerfield, IL: Takeda Pharmaceuticals America Inc; December 2017.
21. Precose [package insert]. Whippany, NJ: Bayer HealthCare Pharmaceuticals; March 2015.
22. Nesina [package insert]. Deerfield, IL: Takeda Pharmaceuticals America Inc; June 2019.
23. Victoza [package insert]. Plainsboro, NJ: Novo Nordisk Inc; June 2019.
24. Jardiance [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals Inc; October 2018.