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CASE REPORT

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Continuous glucose monitoring in an end-stage renal disease patient with diabetes receiving hemodialysis

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Abstract

Diabetes is the leading cause of end-stage renal disease (ESRD) and contributes to heightened morbidity and mortality in dialysis patients. Given that ESRD patients are susceptible to hypoglycemia and hyperglycemia via multiple pathways, adequate glycemic monitoring and control is a cornerstone in diabetic kidney disease management. In ESRD, existing glycemic metrics such as glycated hemoglobin, self-monitored blood glucose, fructosamine, and glycated albumin have limitations in accuracy, convenience, and accessibility. In contrast, continuous glucose monitoring (CGM) provides automated, less invasive glucose measurements and more comprehensive glycemic data versus conventional metrics. Here, we report a 48-year-old male with ESRD due to diabetes receiving thrice-weekly hemodialysis who experienced decreased patient-burden, greater glucose monitoring adherence, improved glycemic parameters, and reduction in hypoglycemia after transitioning to CGM. Through this case, we discuss how CGM is a practical, convenient patient-centered tool that may improve metabolic outcomes and quality of life in ESRD patients with diabetes.

1 | INTRODUCTION

According to the International Diabetes Federation, 463 million adults suffer from diabetes worldwide, among whom ~50% remain undiagnosed (232 million adults).[1] As of 2019, diabetes contributed to 4.2 million deaths and $760 billion in healthcare expenditures worldwide (10% of global healthcare costs). Chronic kidney disease (CKD) is one of the most prevalent complications of diabetes, affecting 30% and 40% of patients with types 1 and 2 diabetes, respectively.[2] Once kidney disease develops, diabetic kidney disease (DKD) patients have more rapid rates of CKD progression versus those without diabetes. Consequently, diabetes is the leading cause of end-stage renal disease (ESRD) in both developed and low-to-middle income countries, and ESRD patients with diabetes have substantially higher morbidity and mortality compared to their non-diabetic counterparts.[3]

Adequate glycemic monitoring and control is a cornerstone in the management of DKD. Even in the absence of diabetes, advanced CKD and ESRD patients are highly susceptible to glycemic derangements.[4] For example, ESRD patients may be prone to hyperglycemia ensuing from insulin resistance, impaired insulin secretion, and exposure to high glucose peritoneal dialysate loads, which is further exacerbated in those with underlying diabetes. Conversely, many non-dialysis dependent (NDD) CKD patients with diabetes transitioning to ESRD may experience spontaneous resolution of hyperglycemia, normalization of glycated hemoglobin (HbA1c) levels, and cessation of anti-diabetes medications due to frequent hypoglycemia in a phenomenon

Yoko Narasaki and Elisa Park are co-first authors.

known as "burnt-out diabetes."[5] Indeed, hypoglycemia is a frequent occurrence in diabetic and non-diabetic NDD-CKD and ESRD patients due to decreased renal gluconeogenesis, impaired insulin degradation and clearance by the kidney and liver, co-existing comorbidities (malnutrition and gastroparesis), uremic toxins, and glucose shifts during hemodialysis,[5,6] and is associated with heightened death risk in these populations.[7]

The achievement of optimal glycemic control in DKD patients has been hindered by the lack of a practical and reliable method for glycemic monitoring in ESRD patients receiving dialysis. In advanced NDD-CKD and ESRD patients, conventional metrics such as HbA1c and self-monitored blood glucose (SMBG) are still predominantly used, despite having a number of limitations with respect to accuracy, convenience, and availability in these populations (Figure 1).[4] However, with the advent of a number of emerging diabetes technologies that are improving healthcare delivery and outcomes in diabetic patients without CKD,[8] there has been growing interest in continuous glucose monitoring (CGM) as a novel and practical tool for glycemic assessment in those with kidney disease. In this case report, we describe a diabetic ESRD patient receiving hemodialysis in whom CGM resulted in improved glycemic control and reduced patient-burden, as well as a brief overview of the advantages, limitations, and future research directions of various glycemic metrics in the DKD population.

2 | CASE DESCRIPTION

The patient is a 49-year-old Hispanic male with ESRD due to diabetes who has received thrice-weekly hemodialysis since 2015. At the age of 26, he was diagnosed with diabetes after presenting with recurrent skin infections and unexplained weight loss. He was initially treated with glyburide which was subsequently changed to metformin, and he was later transitioned to an insulin pump. Over time, the patient developed NDD-CKD which progressed to ESRD, and at the age of 43, he transitioned to thrice-weekly hemodialysis with a tunneled catheter and subsequently an arteriovenous fistula as his vascular access. His diabetes was also complicated by retinopathy with right-eye blindness, neuropathy, Charcot arthropathy, and gastroparesis. His family history was notable for both parents having diabetes, and an aunt and uncle with ESRD presumed to be secondary to diabetes.

Prior to developing ESRD, the patient had utilized SMBG with capillary fingerstick measurements for nearly two decades. During this time, he had wide fluctuations in his glucose levels with asymptomatic hypoglycemia and hyperglycemia, and his HbA1c levels were typically 10%–12% (Figure 2). At the time of transitioning to hemodialysis in 2015, due to poor glucose control and discomfort from capillary fingerstick measurements (limiting his SMBG frequency to once- or twice-daily), his endocrinologist and diabetes educator advised him to use CGM (initially Dexcom G5, later transitioned to Dexcom G6, San Diego, CA). Since transitioning to the CGM, the patient has reported (1) greater adherence to glycemic monitoring, (2) less glycemic variability, (3) increased time-in-target glucose range, and (4) improved HbA1c levels now ranging 6–8% (Figure 3). Furthermore, the patient reports that the ability to view his glucose trends via his smartphone and the availability of patient-alerts for critical glucose levels have led to (5) improved hypoglycemia detection and (6) decreased hypoglycemia frequency. The ease of applying the Dexcom G6 CGM sensor/transmitter and avoidance of painful capillary fingerstick measurements, particularly given his limited vision, has also led to (7) minimal lifestyle interruption, (8) decreased patient burden, and (9) improved quality of life. Given the benefits he has experienced with CGM, he has expressed a strong desire to advocate for the use CGM among other diabetic ESRD patients who may have reservations about embracing new diabetes technologies.

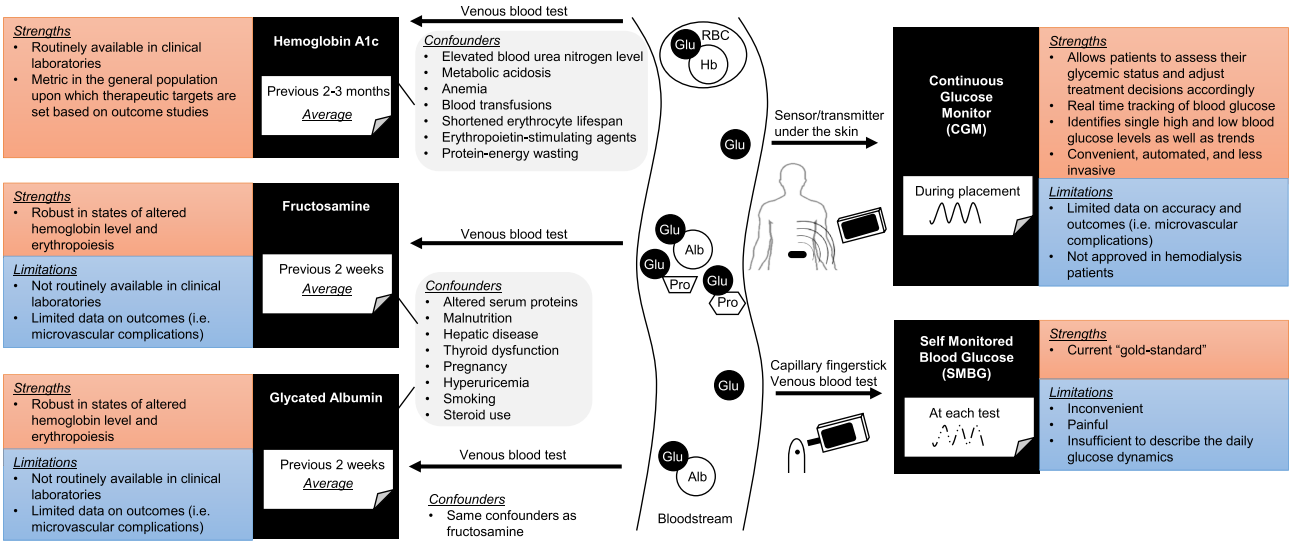

FIGURE 1 Strengths and limitations of various glycemic metrics in diabetic kidney disease [Color figure can be viewed at wileyonlinelibrary.com]

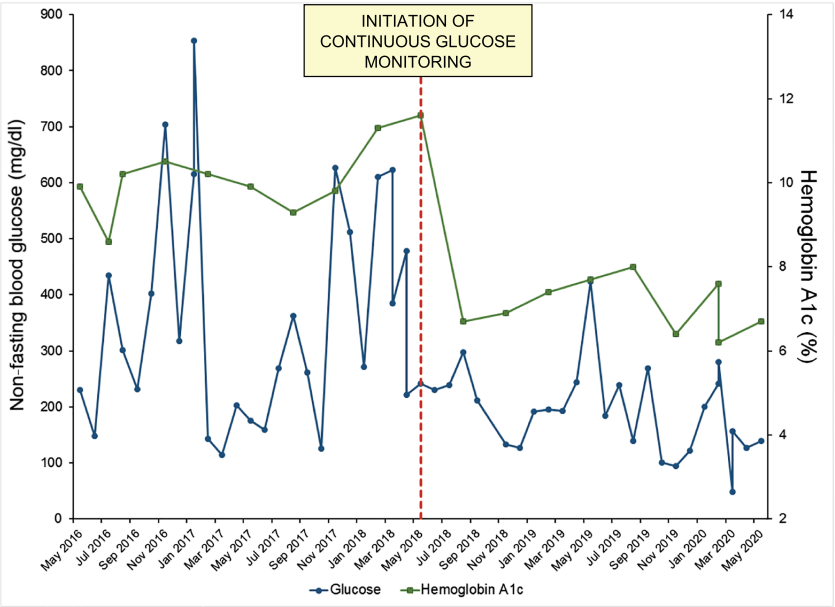

FIGURE 2 The glycemic trajectory of patient with end-stage renal disease and diabetes before and after initiating continuous glucose monitoring. *Y*-axis glucose levels shown in left represent non-fasting blood glucose levels measured during hemodialysis. Dashed line indicates date of continuous glucose monitoring (CGM) initiation [Color figure can be viewed at wileyonlinelibrary.com]

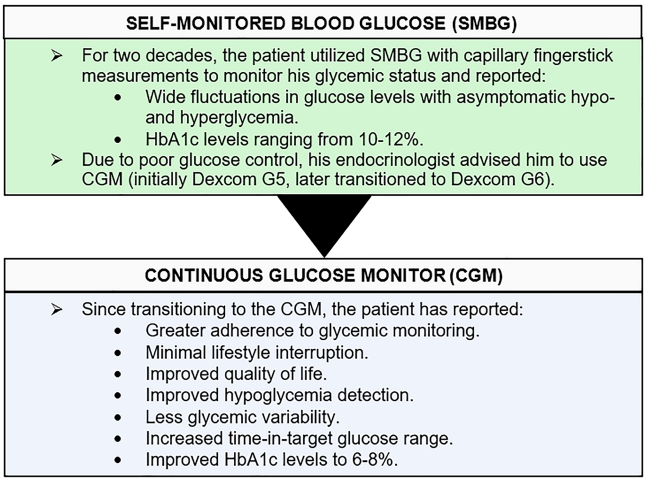

FIGURE 3 Impact on patient's metabolic status and patient-reported outcomes after transitioning from self-monitored blood glucose to a continuous glucose monitor [Color figure can be viewed at wileyonlinelibrary.com]

3 | DISCUSSION

This case report illustrates how CGM may be a practical and convenient patient-centered tool in diabetic ESRD patients with the potential to substantially improve adherence to glycemic monitoring, glucose control, and quality of life beyond that of existing glycemic metrics as described below.

3.1 | CGM technology

A CGM device uses a small subcutaneous sensor that is inserted for a period of 6–14 days to measure interstitial glucose levels.[8,9] Most available sensors measure glucose enzymatically (via glucose oxidase) and provide an indirect measurement of blood glucose as interstitial and blood glucose equilibrate.[10] Real-time CGM devices automatically transmit interstitial glucose values to a patient's receiver or smartphone as frequently as every 5 min, and in addition to presenting a continuous display of glucose levels can also show (1) directional glucose trends and rates of change (allowing patients to pre-emptively adjust their medications and dietary intake) and additional metrics such as (2) glucose variability (i.e., fluctuations in glucose with values ≥ 36% signal hypoglycemia-risk[10,11]), and (3) time-in-range (i.e., proportion of time spent in the target glucose range, time above range, and time below range).[8–10] The Dexcom G6 CGM model used by this patient also allows users to tailor low- and high-glucose thresholds and anticipatory low glucose alerts, and these CGM data and alerts can be remotely shared with others (i.e., care-partners and healthcare providers) via smartphone and data/cloud-based technology.[12]

3.2 | CGM outcomes in patients with diabetes without CKD

There is strong evidence that CGM improves glycemic control, reduces patient-burden, and elevates quality of life in patients with diabetes without underlying CKD. Among patients with type 1 and 2 diabetes receiving insulin, the DIAMOND trial showed that Dexcom-based CGM measurements resulted in reduced hypoglycemia and hyperglycemia, reduced glycemic variability, increased time-in-goal glucose range, greater quality of life, and decreased hypoglycemia-fear compared with SMBG levels using fingerstick testing,[13–19] including in those of elder age (≥65-year-old).[17] Similarly, the HypoDE trial showed that, in comparison to usual care, the use of Dexcom-based CGM resulted in a significant reduction in hypoglycemic events in patients with impaired hypoglycemia-awareness and a

history of severe hypoglycemia.[20] Several meta-analyses of RCTs in patients with type 1 and 2 diabetes have shown that CGM provides greater reduction in HbA1c values with less hypoglycemia as compared with usual care.[21,22]

3.3 | Potential advantages of CGM versus other glycemic metrics

In advanced NDD-CKD and ESRD patients, there are various limitations and uncertainties with existing glycemic metrics, including HbA1c, glycated albumin, fructosamine, and SMBG (Figure 1).[4] As CGM has a number of advantages compared with other glycemic metrics, this glycemic monitoring approach has the potential to lead to a paradigm shift in the clinical management of DKD patients.

HbA1c is the product of a non-enzymatic reaction between glucose and the hemoglobin beta-chain, and it provides an assessment of mean glycemic control over a 120-day period (i.e., average erythrocyte lifespan).[4,9] The strengths of glucose monitoring using HbA1c include its wide availability in clinical laboratories, strong positive correlation with average plasma glucose levels, and the ability to predict microvascular complications. However, the glycation of hemoglobin is influenced by a number of factors that are altered in ESRD (i.e., absolute hemoglobin level, duration of glucose exposure to hemoglobin, pH, and temperature), which may affect the accuracy of HbA1c. The presence of metabolic acidosis and elevated blood urea nitrogen concentrations (leading to carbamylation of hemoglobin, which may be mistaken for glycated hemoglobin by some HbA1c assessment methods) may result in spuriously high HbA1c levels. Conversely, falsely low HbA1c values and underestimation of glycemic levels may be observed with anemia, blood transfusions, frequent utilization of erythropoietin-stimulating agents, or conditions associated with shortened erythrocyte life spans (e.g., hemoglobinopathies, erythrocyte fragility due to uremia, and erythrocyte lysis due to dialysis). Indeed, in a study of 64 dialysis patients with diabetes who underwent concurrent glycemic assessment by HbA1c and CGM, mean blood glucose levels estimated from HbA1c levels were lower than the CGM-measured glucose values.[23] Even in the absence of CKD, the association of mean glucose to HbA1c may show wide variation.[15,24] Furthermore, there are racial differences in glycation, such that HbA1c levels tend to overestimate mean glucose concentrations in Black persons compared with White persons.[25] In addition, as HbA1c provides an average of long-term glycemic status, it may not convey information about episodic hypoglycemia.

Given that plasma proteins also undergo glycation and are unaffected by factors influencing erythrocyte turnover, there has been growing interest in glycated albumin and fructosamine as intermediate markers of glycemic control in CKD.[4,9] Glycated albumin and fructosamine are produced from the non-enzymatic glycation of serum proteins and albumin, respectively, and correspond to mean glycemic control over a 7- to 14-day period. While glycated albumin and fructosamine may also be confounded by non-glycemic factors, including conditions leading to altered serum protein states such as malnutrition, hepatic disease, thyroid dysfunction, pregnancy, hyperuricemia, smoking, and steroid use,[4,9] some data suggest that glycated albumin and fructosamine are more accurate than HbA1c in assessing glycemic status in dialysis patients.[10,26] In addition, there is lack of consensus on standardized measurement methods and universally accepted reference intervals for these metrics.[10]

SMBG using capillary fingerstick and/or venous blood glucose measurements is considered the "gold-standard" for glycemic assessment.[4] Given that more frequent SMBG testing (i.e., at least 10 times daily) has been shown to result in better glycemic control, the American Diabetes Association recommends at least 6–10 daily SMBG measurements in diabetic patients receiving intensive insulin regimens.[27] However, frequent capillary fingerstick measurements may be burdensome, impractical, and painful for patients.[28] Moreover, daily glucose dynamics may not be adequately captured by SMBG, particularly at night or during hemodialysis treatments when blood glucose is seldom measured, thereby failing to detect asymptomatic and nocturnal hypoglycemia and hyperglycemia.

3.4 | CGM: A paradigm shift in the management of DKD patients?

In contemporary clinical practice, the Dexcom G6 CGM device is widely used for glycemic monitoring, and it is approved for use by the Food and Drug Administration in adults and children ages ≥2 years and older with type 1 and 2 diabetes, including patients with NDD-CKD.[12] Indeed, a systematic review of observational studies in dialysis patients with diabetes observed that CGM values correlated moderately with HbA1c levels.[29] As a 2020 Kidney Disease Improving Global Outcomes "Practice Point" (i.e., guidelines in which there is limited evidence and further research is needed), in scenarios where HbA1c accuracy may be uncertain CGM may be used, and CGM metrics such as time-in-range and time-in-hypoglycemia may be considered as alternatives to HbA1c for defining glycemic targets.[9] Notably, in patients with type 1 and 2 diabetes without CKD, the Dexcom G6 CGM has shown good agreement with blood glucose (based on metrics such as the median absolute relative difference, median relative difference, and Clarke error grid analysis).[30,31]

While the Dexcom G6 device is not yet approved in dialysis patients,[10,12] there is ongoing research studying the agreement between this CGM technology versus "gold-standard" blood glucose measurements that aim to confirm the former metric's accuracy in diabetic ESRD patients (ClinicalTrials.gov #NCT04217161).[32] To date, two small pilot studies of diabetic ESRD patients receiving hemodialysis in France have shown that CGM regimens improve short-term glycemic control without increasing hypoglycemia.[33,34] Furthermore, in a prospective study of Japanese hemodialysis patients with diabetes, CGM uncovered a high prevalence (over 20%) of asymptomatic hypoglycemia during hemodialysis treatment.[35] Further large-scale,

rigorous studies are needed to determine whether CGM can improve long-term glycemic control, detection of inter-dialytic and intra-dialytic hypoglycemia and hyperglycemia,[4,6] and other relevant outcomes in diabetic ESRD patients.

4 | CONCLUSION

Growing evidence suggests that CGM provides convenient, automated, and less invasive glucose measurements as compared with conventional approaches. This case report illustrates how CGM is a practical, convenient, patient-centered tool in diabetic ESRD patients with the potential to substantially improve adherence to glycemic monitoring, glucose control, and quality of life. Further studies are urgently needed to determine the comparative effectiveness of CGM versus alternative glycemic assessment methods in advanced NDD-CKD and ESRD patients with diabetes.

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CONFLICT OF INTEREST

CMR and KKZ have received research funding from Dexcom, Inc. DP is an employee of Dexcom, Inc. ANA has served as an investigator for research studies sponsored by NeuroRx Pharma, Pulmotect, Blade Therapeutics, Novartis, Takeda, Humanigen, Eli Lilly, PTC Therapeutics, OctaPharma, Fulcrum Therapeutics, Alexion, and he has served as speaker and/or consultant for BMS, Pfizer, BI, Portola, Sunovion, Mylan, Salix, Alexion, AstraZeneca, Novartis, Nabriva, Paratek, Bayer, Tetraphase, Achogen LaJolla, Millenium, PeraHealth, HeartRite, Aseptiscope, and Sprightly. None of the other authors have relevant disclosures to report.

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