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EDITORIAL

Application and management of continuous glucose monitoring in diabetic kidney disease

Xin-Miao Zhang, Quan-Quan Shen

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Abstract

Diabetic kidney disease (DKD) is a common complication of diabetes mellitus that contributes to the risk of end-stage kidney disease (ESKD). Wide glycemic variations, such as hypoglycemia and hyperglycemia, are broadly found in diabetic patients with DKD and especially ESKD, as a result of impaired renal metabolism. It is essential to monitor glycemia for effective management of DKD. Hemoglobin A1c (HbA1c) has long been considered as the gold standard for monitoring glycemia for > 3 months. However, assessment of HbA1c has some bias as it is susceptible to factors such as anemia and liver or kidney dysfunction. Continuous glucose monitoring (CGM) has provided new insights on glycemic assessment and management. CGM directly measures glucose level in interstitial fluid, reports real-time or retrospective glucose concentration, and provides multiple glycemic metrics. It avoids the pitfalls of HbA1c in some contexts, and may serve as a precise alternative to estimation of mean glucose and glycemic variability. Emerging studies have demonstrated the merits of CGM for precise monitoring, which allows fine-tuning of glycemic management in diabetic patients. Therefore, CGM technology has the potential for better glycemic monitoring in DKD patients. More research is needed to explore its application and management in different stages of DKD, including hemodialysis, peritoneal dialysis and kidney transplantation.

Key Words: Diabetic kidney disease; Continuous glucose monitoring; Glycemic monitoring; Hemodialysis; Peritoneal dialysis; Kidney transplantation

Core Tip: Continuous glucose monitoring (CGM) shows the strength of providing a glycemic profile in diabetic kidney disease (DKD). This article summarizes the use of CGM in early and advanced stages of DKD, including hemodialysis, peritoneal dialysis, and kidney transplantation. CGM may be considered an alternative or complement to measurement of hemoglobin A1c in some contexts.

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INTRODUCTION

Diabetes mellitus (DM) is a chronic disorder characterized by sustained hyperglycemia and its prevalence has caused an increased healthcare burden worldwide[1]. Long-term hyperglycemia and metabolic alterations can lead to various diabetic complications, causing damage to tissues and organs[2]. Diabetic kidney disease (DKD) is one of the major microvascular complications, accounting for 20%-50% among diabetic patients[3]. DKD has been considered as a primary category of chronic kidney disease (CKD) and a leading cause of end-stage kidney disease (ESKD), contributing to the large physical and financial burden globally[4]. DKD is classified in accordance with progressively increased albuminuria (≥ 30 mg/g) and decline in estimated glomerular filtration rate (< 60 mL/min/1.73 m^2)[5].

The risk of hypoglycemia and hyperglycemia is predominantly increased in patients with DKD and particularly at advanced stages. Various factors contribute to glycemic variation in DKD, including impaired renal gluconeogenesis, defective renal clearance of insulin, elevated insulin resistance, and diminished β-cell function[6]. With progressive decline of renal function, initiation of peritoneal dialysis or hemodialysis could markedly affect glycemic variability because the glucose content of dialysates can alter daily glucose profiles[7,8]. The conventional glycemic marker glycated hemoglobin A1c (HbA1c) is limited for the prediction of daily glycemic variability and acute hyperglycemia/hypoglycemia. Moreover, its accuracy and precision are weakened with advanced CKD, and particularly among patients with dialysis. Alternative glycemic indicators, such as glycated albumin or fructosamine, have not been fully validated and applied because the cost and difficulties of implementation in daily practice. Therefore, optimal glycemic control is faced with challenges in patients with DKD.

Continuous glucose monitoring (CGM) is one of the innovative technologies for glycemic monitoring in the past 100 years[9]. CGM devices provide multiple data, including proportion of time-in-target range (TIR), glucose variability and glucose management indicator (GMI), which enable patients to respond immediately prior to acute glycemic events and assist clinicians to adjust appropriate treatment for patients[10]. Two main types of CGM system technologies, real-time CGM (rtCGM) and intermittently scanned CGM (isCGM), are currently available for use. rtCGM systems automatically transmit the data to a receiver, while isCGM systems require the patient to swipe the receiver to access current and historical glycemic files[11]. Emerging studies on the use of CGM suggest its potential for more precise glucose monitoring in patients with DKD compared with other glycemic markers[6,12,13]. The latest Kidney Disease Improving Global Outcomes (KDIGO) guideline advocates that use of CGM may help prevent hypoglycemia and improve glycemic control for patients in whom HbA1c is not compatible with directly measured glycemic levels or clinical symptoms[14].

APPLICATION OF CGM IN NONDIALYSIS PATIENTS WITH DKD

Various studies have assessed correlation between CGM metrics and conventional glycemic markers including HbA1c, glycated albumin and fructosamine during different DKD stages. The beneficial effect of CGM on glycemic control in patients with early stages of CKD is comparable to that in the general population with diabetes. With decreased renal function, the accuracy of HbA1c tends to fall in advanced DKD, partly due to anemia and treatment with iron supplements or erythropoietin-stimulating agents[15,16].

A recent study by Lu *et al*[17] has assessed the association between HbA1c and CGM metrics among patients with different stages of DKD. The correlation between HbA1c and GMI was attenuated with impaired renal function as shown in patients with CKD KDIGO 1-2 stages (r = 0.576) and stage 3 (r = 0.266). HbA1c was not significantly correlated with GMI in CKD KDIGO 4-5 stages (r = 0.296, P = 0.079). Ling *et al*[18] also evaluated the relationship between HbA1c and CGM metrics in moderate-to-advanced DKD (CKD KDIGO 3b to 5), which found correlations between GMI and HbA1c attenuated with advancing DKD [CKD KDIGO 3b (r = 0.68), CKD KDIGO 4 (r = 0.52), CKD KDIGO 5 (r = 0.22)]. HbA1c did not correlate with duration of hypoglycemia in any DKD stage, although it may have been associated with TIR and time in hyperglycemia in DKD (CKD KDIGO 3b-4). Likewise, Lo *et al*[19] indicated that HbA1c correlated well with mean CGM glucose in CKD KDIGO 3 (r = 0.79) but gradually weakened in CKD KDIGO stage 4-5 (r = 0.34). Vos *et al*[20] also observed poor correlation between HbA1c and CGM in DKD (CKD KDIGO stage 4-5, r = 0.38), while they found glycated

albumin correlated significantly with CGM mean glucose in patients with DKD (CKD KDIGO stage 4-5, r = 0.54). Therefore, their study suggested that glycated albumin is more accurate for assessment of glycemia compared with fructosamine and HbA1c in advanced DKD. However, a recent prospective cohort study conducted by Zelnick *et al*[12] suggested that HbA1c is no more variable and less biased than glycated albumin and fructosamine in patients with DKD (CKD KDIGO stage 3-5). They observed similar correlations of these glycemic biomarkers with CGM mean blood glucose among patients with DKD (CKD KDIGO stage 3-5) (HbA1c, r = 0.78; glycated albumin, r = 0.78; fructosamine, r = 0.71), but none of them captured any incidence of acute glycemic variability as indicated by CGM devices. Oriot *et al*[21] investigated the discordance between HbA1c and CGM-derived metrics in DKD individuals, which showed higher HbA1c levels in this population and suggested that GMI data are more precise for monitoring glycemia. Similarly, Yoshii *et al*[22] reported that higher HbA1c levels did not always protect against hypoglycemic episodes as performed by CGM devices. CGM-measured hypoglycemia is frequent in patients with DKD or CKD without diabetes[23,24]. Ushiogi *et al*[24] observed that only two hypoglycemia symptoms were reported among 366 patients during CGM measurements, but hypoglycemia occurred in 41% of DKD participants and 48% of CKD patients without diabetes according to CGM detection. Similarly, a retrospective cohort study performed in 823 diabetic patients indicated that hypoglycemic events were negatively correlated with renal function, suggesting the role of TIR, especially nocturnal TIR, in the evaluation of DKD progression[25]. Apart from deficient kidney gluconeogenesis and counter regulatory hormone responses, hypoglycemic incidence is associated with impaired clearance of antidiabetic agents such as insulin and/or sulfonylureas [26]. Therefore, using CGM-derived metrics to complement HbA1c analysis is beneficial for patients with DKD and treated with insulin and/or sulfonylureas to avoid hypoglycemic episodes regardless of HbA1c levels. The Pearson correlation between CGM metrics and glycemic biomarkers on different stages of CKD in diabetic patients is summarized in Table 1.

APPLICATION OF CGM IN DIABETIC PATIENTS ON DAILYSIS

Diabetic patients with ESKD have a wide glycemic variability during dialysis. Patients treated by hemodialysis have an increased risk of hypoglycemia, while patients with peritoneal dialysis more frequently have hyperglycemia[27]. The KDIGO 2022 guideline highlights that the precision of HbA1c falls with advanced CKD, particularly among patients treated by dialysis[14]. However, currently there is no consensus on CGM use in diabetic patients treated by dialysis.

Emerging studies have investigated CGM in the context of DKD with hemodialysis. CGM may improve glucose control and optimize therapeutic adjustments without increased risk of hypoglycemia[28]. The mean absolute relative difference (MARD) is commonly used to assess the accuracy of CGM sensors and MARD with good accuracy should be < 10% as recommended[29]. A recent study by Avari *et al*[30] compared the real-time and isCGM in 40 patients undergoing hemodialysis, and suggested that isCGM (MARD 11.3%) was more reliable than rtCGM (MARD 22.7%) for glucose monitoring. Hissa *et al*[31] showed that interstitial glucose detection by CGM devices was in good concordance with capillary measurements at the beginning of the dialysis session (MARD 16.5%-19%). The correlation, however, was weakened in later sessions (MARD 25.3%-28.8%), probably due to increased inflammatory response to sensor insertion, loss of dialysis fluid, weight changes between dialysis sessions, and anemia. In line with the study of Hissa *et al*[31], another study of 41 participants undergoing hemodialysis demonstrated that the accuracy of CGM sensor glucose levels deteriorated with duration of use from the first week (MARD 13.8%-21%) to the second week (MARD 24.5%-36.1%)[32]. They observed that MARD correlated negatively with dry weight, body mass index, hemoglobin and hematocrit after hemodialysis, which may have affected the differences between CGM and capillary glucose levels. In addition, Villard *et al*[33] compared the accuracy of CGM with capillary and venous blood glucose measurements in 20 diabetic patients on hemodialysis (MARD 13.8% and 14.4%, respectively), suggesting overall performance of CGM appears reasonably accurate and relevant for clinical use. However, MARD does not provide information about dynamic changes in glycemia or hypo-/hyperglycemia incidence; therefore, it should not be used as the sole parameter to evaluate CGM systems[34]. The study by Hayashi *et al*[7] found great glycemic variability during hemodialysis and > 20% of the participants experienced asymptomatic hypoglycemia, which is more frequent than currently recognized. Compared with HbA1c and glycated albumin, CGM values favors physicians for awareness of hemodialysis-related hypoglycemia. Bomholt *et al*[35] also investigated glycemic variations on and off dialysis in patients with T2DM using CGM. They observed that patients developed intradialytic hypoglycemia despite the use of glucose-containing dialysate, indicating that hypoglycemia is a risk during hemodialysis. The hemodialysis-related hypoglycemia may be associated with increased erythrocyte uptake of glucose and improved insulin sensitivity due to alleviation of uremia and correction of acidosis[36,37]. The use of CGM contributes to avoiding hypoglycemic events in hemodialysis, which are frequently asymptomatic and potentially severe. However, the accuracy of CGM should be improved with the progress of hemodialysis and further studies are needed to avoid influencing factors as mentioned above.

Glucose-based dialysate containing 100-300 g glucose is widely used in peritoneal dialysis. Therefore, patients undergoing peritoneal dialysis are prone to hyperglycemia due to glucose absorption from dialysate *via* the peritoneal cavity[38]. Additionally, with increasing use of glucose substitute dialysate and insulin treatment, peritoneal dialysis patients are also at risk of developing hypoglycemia. CGM may contribute to detection of asymptomatic glucose variations by hypertonic exchanges in this population. A recent study by Ng *et al*[8] showed rtCGM detection rates for hyperglycemic and hypoglycemic events were 96.5% and 60%, respectively. They suggested the accuracy and reliability of rtCGM across a wide range of glucose levels in peritoneal dialysis patients (MARD 10.4%). Notably, its accuracy was not affected by acidosis, urea levels and volume overload. Likewise, Ling *et al*[39] demonstrated that rtCGM detection was accurate in peritoneal dialysis with an overall MARD of 10.4%, and almost not influenced by overloaded volume,

Table 1 The Pearson correlation between continuous glucose monitoring metrics and glycemic biomarkers on chronic kidney disease (number of participants)

CKD stages	1-2	3a	3b	4	5	Ref.
HbA1c	0.576 (64)	0.266 (56)	0.266 (56)	0.296 (36)	0.296 (36)	Lu *et al*[17]
			0.68 (33)	0.52 (43)	0.22 (14)	Ling *et al*[18]
		0.79 (14)	0.79 (14)	0.34 (29)	0.34 (29)	Lo *et al*[19]
				0.38 (25)	0.38 (25)	Vos *et al*[20]
		0.78 (80)	0.78 (80)	0.78 (80)	0.78 (80)	Zelnick *et al*[12]
Glycated albumin				0.54 (25)	0.54 (25)	Vos *et al*[20]
Fructosamine		0.78 (80)	0.78 (80)	0.78 (80)	0.78 (80)	Zelnick *et al*[12]
		0.71 (80)	0.71 (80)	0.71 (80)	0.71 (80)	Zelnick *et al*[12]

CKD: Chronic kidney disease; HbA1c: Hemoglobin A1c.

body composition and anemia. Similar to those in hemodialysis, HbA1c is incapable of indicating acute glycemic variations that frequently occur in this population. Qayyum *et al*[40] observed that a high incidence of asymptomatic hypoglycemia was detected by CGM, but not reflected by HbA1c. They found three of 15 patients with HbA1c > 9% still had significant hypoglycemia. Additionally, the study of Bomholt *et al*[41] showed that mean glucose level was underestimated by HbA1c when compared with CGM, indicating the strength of CGM in glycemic control in peritoneal dialysis patients. A number of factors such as glucose concentration of dialysate, dwell time, and peritoneal membrane transport status may affect glycemic pattern during peritoneal dialysis[42]. Research on CGM in the peritoneal dialysis population may provide comprehensive glycemic profiles and facilitate individualized therapeutic adjustment.

APPLICATION OF CGM IN KIDNEY ALLOGRAFT RECIPENTS

Perioperative and post-transplant hyperglycemia is common and severe in kidney allograft recipients because > 20% of them have ESKD caused by long-term diabetes. Strict glycemic control is crucial for patients to prevent *de novo* post-transplant diabetes or complications of previous diabetes in the transplanted kidney and direct glucose monitoring is more beneficial for providing information on glycemic variability and warning of acute incidents[43]. Jo *et al*[44] investigated CGM applied by participants 2 wk before and 2 wk after kidney transplantations. The CGM system provided an overall hyperglycemic profile, which showed a hyperglycemic tendency, higher mean glucose levels and increased GMI from before to after intervention. A randomized study of 40 patients assessed the use of CGM devices during the first 5 d after kidney transplantation, suggesting that CGM significantly reduced the incidence of hyperglycemic episodes and median glucose levels without increasing hypoglycemic events[45]. Similarly, Jin *et al*[46] investigated glucose profiles and the degree of hyperglycemia after kidney transplantation for 1 month. They observed hyperglycemia over fasting or postprandial glucose standard occurred in 42.1% during the early period after operation, except for patients with pre-existing diabetes. However, more studies involving CGM performance at regular intervals based on different perioperative and post-transplant times are needed.

CONCLUSION

The present study reviewed the application of CGM in diabetic patients with different stages of CKD, including patients treated with hemodialysis, peritoneal dialysis or kidney transplantation. CGM provided a more precise and comprehensive estimation of mean glucose and glycemic variability, and had benefits in indicating acute episodes of hyper- or hypoglycemia. Therefore, the use of CGM is suggested as an alternative or complement to conventional glycemic indicators. Nevertheless, there is currently insufficient evidence to support the use of CGM in patients on dialysis or with kidney transplantation. Further clinical trials are required to improve and standardize its application for effective glycemic management and therapeutic regimen adjustment.

FOOTNOTES

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