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Beneficial Recognition of Glucose Variability for Adequate Lifestyle by Continuous Glucose Monitoring (CGM)

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Abstract

Recently, actual changes in blood glucose can be measured by continuous glucose monitoring (CGM) using FreeStyle Libre. The case involves a 67-year-old male patient with type 2 diabetes (T2D) treated with Multiple Daily Insulin (MDI) therapy, who underwent CGM. Analysis of the CGM data revealed that hyperglycemia resulted from increased carbohydrate intake and irregular meal timings and quantities. The estimated HbA1c from CGM was 6.6%, whereas the HbA1c value recorded at the outpatient clinic during the same period was 7.3%. The use of CGM applications encourages diabetic patients to be mindful of their carbohydrate intake in daily life, leading to an increased ratio of time spent in the target range (TIR).

Keywords

Continuous Glucose Monitoring (CGM), Freestyle Libre, Multiple Daily Insulin (MDI), Low Carbohydrate Diet (LCD), Time in Range (TIR)

Abbreviations

CGM: Continuous Glucose Monitoring; MDI: Multiple Daily Insulin; LCD: Low Carbohydrate Diet; TIR: Time in Range

Introduction

From the global perspective of diabetes by the World Health Organization (WHO), the increasing burden of diabetes-related medical and health issues has garnered significant attention [1]. Among these, specific targets and metric levels have been identified for certain United Nations (UN) members, which encompass the diagnosis of diabetes, glucose variability, HbA1c control, complications of cardiovascular diseases, and dyslipidemia. Consequently, diabetes has emerged as a crucial issue, exerting diverse influences on medical, clinical, social, and economic fields [2]. In terms of total expenses, diagnosed diabetic patients require over $400 billion annually in the US, with estimates of over $300 billion for direct costs and over $100 billion for indirect costs [3].

Regarding diabetic treatment, recent advancements have focused on detailed measurements of

simultaneous glucose variability, effective oral hypoglycemic agents (OHAs), and injective agents for diabetes. Furthermore, some agents demonstrate beneficial clinical effects on heart failure, blood pressure, and renal function, leading to a reduced risk of cardiovascular events [4]. These diabetic medications include sodium-glucose co-transporter 2 inhibitors (SGLT2-i), glucagon-like peptide-1 receptor agonists (GLP-1RA), newer glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 dual agonists, among others.

Additionally, detailed glucose variability can be detected through the use of continuous glucose monitoring (CGM) [5]. Several studies have compared the clinical effects of CGM versus self-monitoring of blood glucose (SMBG). These studies have demonstrated significantly higher time in range (TIR) with CGM compared to SMBG, as well as a predominance of time above range (TAR), time below range (TBR), and mean difference (MD) [6]. To examine CGM perspectives in primary care medicine, 10 studies encompassing 4006 participants were reviewed for CGM and intermittent scanning CGM (is-CGM) [7]. The results indicated that CGM exhibited greater efficacy in reducing HbA1c with a weighted mean difference (WMD) of -0.43% compared to usual care measurements. CGM and is-CGM can improve TIR, TAR, and TBR over standard care. However, potential clinical challenges include biases such as unmasking, short duration, or sponsorship by specific industries.

Our team, led by Authors et al., has dedicated years to medical research on diabetic examination and treatment, including type 2 diabetes (T2D), type 1 diabetes (T1D), and slowly progressive insulin-dependent diabetes mellitus (SPIDDM), among others [8]. Among our contributions, we have proposed the beneficial aspects of a low carbohydrate diet (LCD) and practical methods such as super-LCD, standard-LCD, and petite-LCD [9]. Concurrently, we have established the Japan LCD Promotion Association (JLCDPA) with various initiatives [10]. Furthermore, clinical research on detailed glucose variability using CGM has been conducted [11]. In this report, we present an insightful diabetic case involving multiple daily insulin (MDI) treatment, outlining the general situation and providing perspectives on this case.

Case Presentation

Medical History:

The current case involves a 67-year-old male patient with T2D. He had no significant past medical history and was diagnosed with diabetes at the age of 45. In terms of family history, both his father and mother were positive for diabetes.

Over the years, he had been prescribed various oral hypoglycemic agents (OHAs). By the time he reached his 60s, he initiated insulin therapy for MDI, and his condition has remained relatively stable, with his HbA1c consistently around 6.7-7.1% for years.

His diabetic regimen included Ipragliflozin L-proline 50mg, Rosuvastatin 2.5mg, and Valsartan 80mg per day as oral medications. Additionally, insulin treatment consisted of Degludec 10 units at 21:00 hours, and NovoRapid insulin 8-8-8 units three times daily just before meals.

Physical Examination:

This case presented with no notable findings on physical examination, with vital signs, speech, and consciousness all within normal limits. He measured 173 cm in height, weighed 76 kg, and had a body mass index (BMI) of 25.4 kg/m^2. Examination of the chest and abdomen revealed no abnormalities.

In terms of diabetic complications, he has had retinopathy for years, which was associated with blurred vision, leading to a diagnosis of pre-proliferative retinopathy. While diabetic neurological motor and sensory disturbances were not evident, he did experience episodes of calf cramps during sleep, indicative of diabetic neuropathy. To address these symptoms, in addition to his prescribed insulin and oral agents, he was also provided with Chinese medicine for occasional calf cramps.

Clinical Progress:

Regarding diabetic nephropathy, the estimated glomerular filtration rate (eGFR) was approximately 41-48 mL/min/1.73m^2, with no increased albuminuria.

He has been regularly undergoing basic standard laboratory exams. Among these, the most recent four consecutive biochemical results are summarized in **Table-1**. These results displayed elevated levels of HbA1c, blood glucose, and serum creatinine, indicating the presence of diabetes and chronic or diabetic renal failure.

Table-1: Change in Laboratory Data

		2023			2024	Units
		Jan	May	Sept	Jan	
Liver	AST	12	13	15	14	(U/L)
	ALT	14	15	16	16	(U/L)
	GGT	27	29	24	24	(U/L)
Diabetes	HbA1c	7.6	7.9	7.6	7.8	(%)
	Glucose	181	178	156	163	(mg/dL)
CBC	WBC	51	72	56	60	(x10*2/μL)
	RBC	478	484	504	453	(x10⁴/μL)
	Hb	14.7	14.9	15.2	14.0	(g/dL)
	PLT	20	17	17	20	(x10⁴/μL)
Lipids	HDL	52	54	55	48	(mg/dL)
	LDL	83	80	81	84	(mg/dL)
	TG	92	133	124	104	(mg/dL)
Renal	BUN	16	27	31	21	(mg/dL)
	Cre	1.23	1.60	1.30	1.15	(mg/dL)
	UA	6.4	5.8	6.1	6.0	(mg/dL)

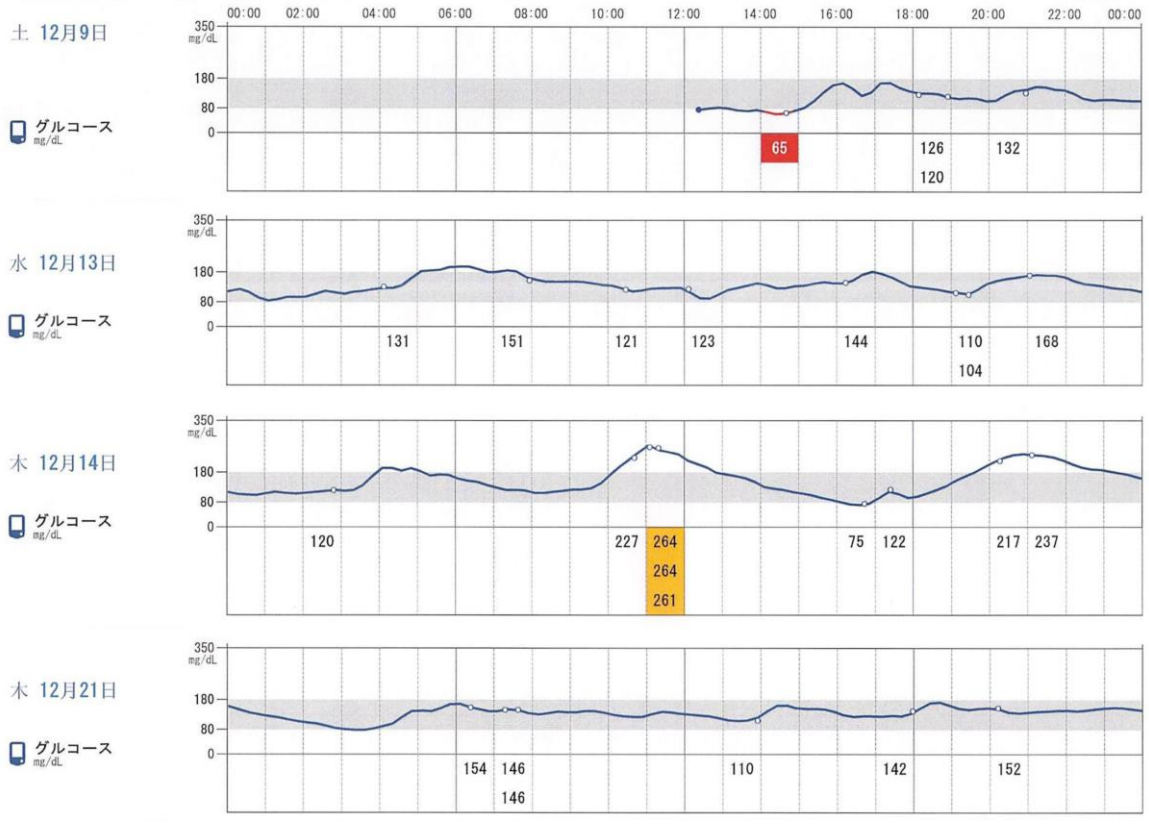

Fig-1: Blood Glucose Profile by CGM Ssing Freestyle Libre for 2 Weeks

Results

To facilitate appropriate diabetic treatment, daily blood glucose variability was assessed through CGM measurements using the FreeStyle Libre device. This device allows for monitoring of detailed glucose changes every 15 minutes. The analysis was conducted for a period of 2 weeks in December 2023, and data from 14 days are illustrated in **Fig-1**. Four representative patterns were selected, depicting lower hypoglycemia, a relatively stable case, three peaks of hyperglycemia, and an ideal example within the normal range.

Fig-2 presents the average glucose variability observed in CGM. Three peaks are evident, correlating with the three meals consumed each day. The blood glucose levels range mostly between 80 mg/dL to 180 mg/dL. The estimated HbA1c value over the 14-day period was calculated to be 6.6%. In contrast, the HbA1c level measured at the outpatient clinic during November to December 2023 was 7.3%. This discrepancy indicates a difference of 0.7% between the actual HbA1c and the estimated HbA1c obtained from the FreeStyle Libre CGM device.

Ethical Considerations

This report has been fundamentally described following the ethical principles of the Helsinki Declaration. Additionally, it adheres to standard Ethical Guidelines for Human Research. The current investigation was conducted with the oversight of an ethical committee established by the authors and colleagues. This committee comprises several professional specialists, including the hospital director, doctors, head nurse, pharmacist, dietitian, and legal expert. Extensive discussions were held regarding medical and ethical matters, leading to an agreement on the protocol. The patient provided informed consent prior to participation.

Discussion

Over the decades, various practices and research have focused on overweight, T2D, the Diabetes Remission Clinical Trial (DiRECT), and metabolomics technologies [12]. Several biomarkers potentially related to diabetic pathophysiology of complications and clinical progress have been identified, such as LDL, triglycerides, branched-chain amino acids (BCAAs), and other metabolites. Recent advancements in clinical development include the simultaneous measurement of blood glucose changes using CGM. Notably, there has been rapid development in CGM technology in recent years, with the FreeStyle Libre device becoming popular and widely used in diabetic practice and research.

For a prospective observational cohort study, T2D adults receiving insulin treatment were included in the protocol [13]. The primary outcome focused on Time in Range (TIR) for blood glucose levels of

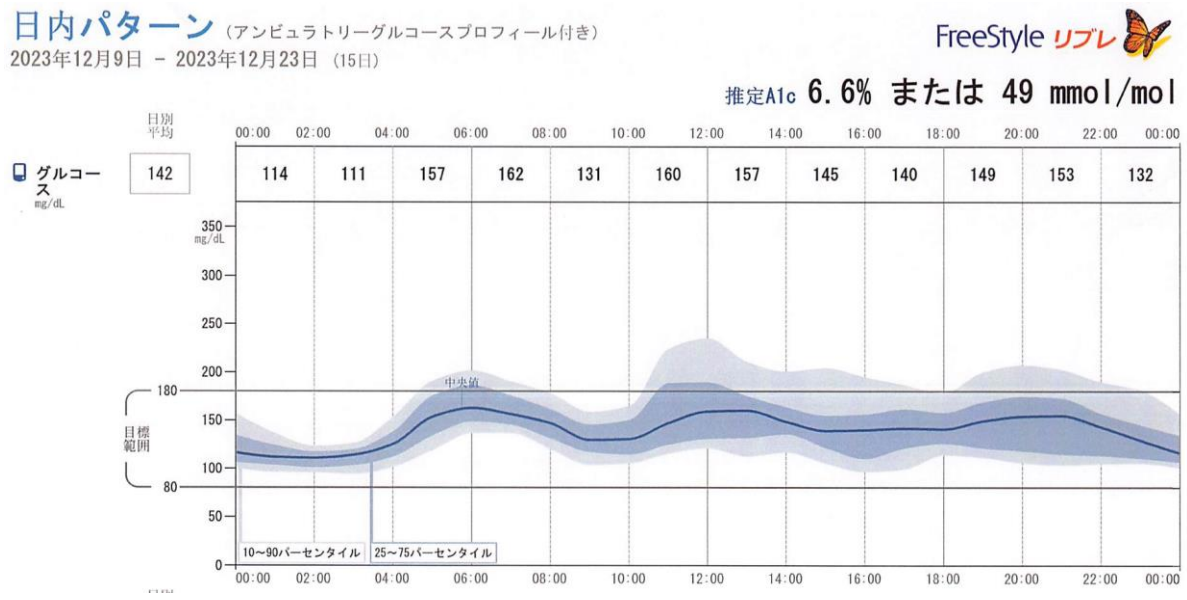

Fig-2: Changes Blood Glucose Variability in Average by CGM for 2 Weeks

70-180 mg/dL. The study involved 566 participants who completed 6 weeks of CGM monitoring, with an average age of 72.8 years, BMI of 27.8 kg/m^2, and HbA1c of 8.0%. The comparison data showed TIR percentages ranging from 63.5% to 65.5%, Time Below Range (TBR) from 5.8% to 3.8%, and glucose variability from 34.9% to 33.0%, respectively.

Various studies have compared CGM with real-time (rt)-CGM. Combining results from 9 rt-CGM and 5 flash glucose monitoring (FGM) studies, a statistically significant decrease in HbA1c of -0.32% was found [14]. Both flash CGM and rt-CGM demonstrated statistically significant lower HbA1c levels. However, Randomized Controlled Trials (RCTs) were of short duration, indicating the need for longer investigations to assess clinical outcomes. A review of 12 recent RCTs with 1248 participants examined 8 rtCGM and 4 intermittently scanned (is)-CGM studies [5]. Various markers were assessed, including TIR, TBR, glycemic variability, and HbA1c. Compared to self-monitoring of blood glucose (SMBG), CGM showed a predominance of data, including a mean difference (MD) in HbA1c of -0.31% (-3.43 mmol/mol). Furthermore, rtCGM demonstrated a larger effect, with an MD of -0.36%, TIR of 6.36%, TBR of -0.66%, and glycemic variability of -1.47%. A comparison study on blood glucose measurements between FGM and point-of-care (POC) measurement was conducted, revealing that glucose values from FGM were lower than those from POC by 27 mg/dL (1.5 mmol/L, $p<0.001$) [15]. This trend has been consistently observed in differences between estimated HbA1c values from FGM and laboratory blood glucose and/or HbA1c.

In this report, the daily fluctuations in blood glucose over 4 days were presented, with each change attributed to irregular meal content and timing, leading to unstable blood glucose variability. Post-prandial elevation of blood glucose was primarily due to carbohydrate-rich meals. The patient noted that hyperglycemia seemed to occur after consuming meals with higher carbohydrate content. Adjusting to a diet with fewer carbohydrates or consuming meals more slowly resulted in decreased glucose fluctuation. Based on the unstable CGM data, the patient understood the situation and aimed to adopt a more stable approach to nutritional treatment.

This case involves a 67-year-old male with T2D and diabetic nephropathy, characterized by elevated serum creatinine, who has been treated with MDI for years [16]. Several limitations exist in his medical history, diagnosis, and treatments, including his overall health condition, diabetic complications, CGM application, evaluation of various aspects, and treatment combinations. Moving forward, improvements in the accuracy of devices like the FreeStyle Libre 3 are expected to provide benefits in clinical practice [17].

In summary, this report presents a case study of a 67-year-old male with T2D who underwent glucose monitoring by CGM and received MDI treatment, offering insights into various perspectives. It is hoped that this article will provide useful information for diabetic research and clinical practice.

Conflict of Interest

The authors have read and approved the final version of the manuscript. The authors have no conflicts of interest to declare.

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Keywords: Continuous Glucose Monitoring (CGM), Freestyle Libre, Multiple Daily Insulin (MDI), Low Carbohydrate Diet (LCD), Time in Range (TIR)