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Useful Measurement of Glucose Variability by Flash Glucose Monitoring (FGM) with the Efficacy of Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitor

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Abstract

Diabetes has been a crucial medical and social problem worldwide. For adequate nutritional therapy, there have been discussions concerning Calorie Restriction (CR) and Low Carbohydrate Diet (LCD). We have investigated glucose variability of diabetic patients applying CR, LCD, continuous glucose monitoring (CGM) and applied FreeStyle Libre which is flash glucose monitoring (FGM). The patient is a 40-year-old female with type 2 diabetes mellitus (T2DM), who showed BMI 20.7, postprandial blood glucose 257 mg/dL. HbA1c 12.1%, Glycoalbumin 31.6% (11.6-16.4), serum C-peptide 2.0 ng/ml and unremarkable data of liver function, renal, lipids. She was provided the intervention of three stages, which are i) CR with 60% carbohydrate in Day 1-2, ii) LCD meal with 12% carbohydrate in Day 3-5; iii) LCD + Sodium-glucose cotransporter 2 (SGLT2) inhibitor (Ipragliflozin L-Proline 50mg) in Day 6-12. The glucose profile was measured by FreeStyle Libre Pro (Abbott) for 14 days. The daily profile of blood glucose was abruptly decreased on Day 6. Time percentage of satisfactory blood glucose 70-180 mg/dL (/24h) was 0%, 0%, 2%, 14%, 0%, 54%, 100% in Day 1-7, respectively. These results suppose the acute clinical efficacy of SGLT2 inhibitor, and this report would become a reference for future diabetic practice and research.

Keywords

Low Carbohydrate Diet; Continuous Glucose Monitoring; FreeStyle Libre Pro; Flash Glucose Monitoring; Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitor; Japan LCD Promotion Association (JLCDPA)

Abbreviations

LCD: Low Carbohydrate Diet; CGM: Continuous Glucose Monitoring; FGM: Flash Glucose Monitoring; T2DM: Type 2 Diabetes Mellitus; SGLT2: Sodium-Glucose Cotransporter 2; CR: Calorie Restriction

Introduction

In recent years, diabetes has been an important medical and social problem in the world. For adequate treatment of Type 1 and Type 2 Diabetes Mellitus (T1DM, T2DM), detail blood glucose variability can be measured and evaluated. In diabetic practice, continuous glucose monitoring (CGM) has been introduced and developed for years. CGM system has revealed various useful efficacy and influences [1]. Furthermore, it shows beneficial self-efficacy and other positive attitudes from advanced technology [1]. In several reports, it could detect minute glucose changes by preventing hypoglycemic episodes and other harmful events [2].

CGM has been prevalent in clinical practice and evaluated for a useful method in order to optimize glucose variability in diabetes [3]. When the patients are in the program of low carbohydrate diet (LCD), CGM can become beneficial apparatus for the target of glycemic control with professional management [3].

The fundamental therapy for T1DM and T2DM would be nutritional treatment. Historically speaking, calorie restriction (CD) (low-fat) meal was formerly broadly conducted for usual therapy. However, the effect had not been so satisfactory. Successively, Bernstein and Atkins presented the new nutritional method of LCD. LCD has been prevalent in North American and European countries until now [4]. After that, many useful results for LCD have been observed so far with the beneficial effects of LCD. Among them, the report from Dietary Intervention Randomized Controlled Trial (DIRECT) Group reported the actual efficacy of LCD for 2 years and 4 years with medical evidence [5,6]. There have been many reports suggesting the predominance of LCD rather than CR until now [7-9].

On the other hand, LCD was initiated in Japan by the author and colleagues [10]. After that, our group has continued clinical practice and research and educational seminars for developing LCD information and practice. Furthermore, we have established the Japan LCD Promotion Association (JLCDPA) for a social movement of adequate anti-aging medicine. Among them, we have educated many people on how to continue LCD successfully, which is the application of three types of LCD. Those are super-LCD, standard-LCD, and petite LCD, including carbohydrate ratio of 12%, 26%, 40%, respectively [11]. Our group investigators have clarified the physiological beneficial role from hyperketonemia in the axis of a pregnant mother, newborn, placenta and fetus [12]. Furthermore, a comparison of the daily profile of glucose variability on CR and LCD has investigated, and CR breakfast with 70g of carbohydrate has been utilized for meal tolerance test (MTT) similar to 75gOGTT [13,14].

For several years, the detail measurement of blood glucose variability has been possible. The technology has been continuous glucose monitoring (CGM) systems in the diabetic practice [15]. After that, flash glucose monitoring (FGM) has been introduced with higher technology. Thus, the medical apparatus FreeStyle Libre Pro has been prevalent bringing easier management for analysis of glucose fluctuation [16].

Our group has continued FGM studies, and we experienced a T2DM case with medically interesting progress using FGM and sodium-glucose co-transporter 2 (SGLT2) inhibitors. Then we report the case and discuss s in this article.

Case Presentation

History of Present Illness:

The case was a 40 years-old female. She was diagnosed as T2DM about 11 years ago. At that time, she was pointed out to be diabetic when she received an annual check-up. She has a negative family history for diabetes or particular diseases. About 4 years ago, she revealed a rather higher HbA1c value and has treated for T2DM by anti-diabetic oral medicine for a

few months. After that, she did not visit the clinic for the treatment of T2DM.

After 3 years follow up the natural course without therapy, she was advised to visit diabetologist because of elevated HbA1c value.

Clinic Visits and Examination Results:

She visited the diabetes department of the clinic. Her physicals and vitals were unremarkable. Her stature showed 162 cm and 54.5 kg, and her body mass index (BMI) was 20.7 kg/m^2.

There are several routine examinations for diabetes, including postprandial blood glucose 257 mg/dL, HbA1c 12.1%, Glycoalbumin 31.6% (11.6-16.4) and serum C-peptide 2.0 ng/ml. Two weeks after her first contact, she was admitted for detail evaluation and treatment of LCD.

General Examination:

Urinalysis showed the following results: protein negative, sugar strongly positive, urobilinogen negative, occult blood negative. Occult blood in stool was negative. Chest X-ray and ECG were within normal limits. Echograms of the carotid artery, heart and abdomen were unremarkable.

Blood Biochemistry:

Blood test showed the following: Complete blood count (CBC); WBC 4900/μl, RBC 503 x 10^4/μl, Hb 13.5 g/dL, CRP 0.03 mg/dL, BUN 16 mg/dL, Cre 0.6 mg/dL, Uric Acid 6.1 mg/dL, total protein 7.2 g/dL, Albumin 4.3 g/dL, AST 19 IU/mL, ALT 20 IU/mL, LDH 162 IU/mL, r-GTP 17 IU/mL, Triglyceride 101 mg/dL, HDL-C 69 mg/dL, LDL-C 173 mg/dL.

Diabetes-related Exams:

There are several data about diabetes as follows: i) anti-GAD antibody < 0.5 (< 0.5), ii) Urinary sugar (g/day) was 47.7g, 17.2, 6.8g and 52.1g/day, in day 3,4,5,6, respectively. Its normal range is less than 0.15 g/day. LCD was provided on day 3-14. SGLT2-inhibitor agent was given in day 6, iii) On day 14, her blood glucose was 78 mg/dL in fasting 0700h, and 91 mg/dL in 2 hours after lunch, iv) Ketone body in blood was 3394 μmol/L (< 76) on day 14.

Meals of CR and LCD:

She was provided the usual CR meal for days 1 and 2. After that, she was on LCD from day 3 to day 14. The nutritional content of CR has been from the nutrient balance of the Japan Diabetes Society (JDS). It is standard balance with protein 15%, fat 25% and carbohydrate 60% [17].

The protocol of LCD was provided from day 3 to day 14. The LCD content was 1400 kcal/day, and the carbohydrate ratio was 12% [11]. By the calculation, carbohydrate intake is 1400 x 0.12 = 168 cal/day by the intake of carbohydrates. It equals to 42 g of carbohydrate per day.

FGM System:

In order to study the detailed blood glucose variability, the FGM system was applied. The apparatus was FreeStyle Libre Pro, which has been introduced to clinical practice [18]. It has been produced by Abbott Diabetes Care Inc., Alameda, CA, USA [15]. As this apparatus has shown reliable results in clinical trials, it has been evaluated as simple and beneficial for detecting blood glucose movement simultaneously [16].

The detail blood variability was studied for 14 days. Regarding the evaluation of blood variability, the normal range of glucose was considered satisfactory range as the level between 70 mg/dL to 180 mg/dL. When the blood glucose is within the normal range, a satisfactory time percentage would be 100%. If the blood glucose would be always more than 180 mg/dL for 24 hours, the percentage would be 0%.

Results

The detailed profile of blood glucose variability was studied by FGM (**Fig-1**). On days 1 and 2, the meal was usual CR with 60% of carbohydrates. Average blood glucose was more than 300 mg/dL, and the time percentage of glucose level more than 180 mg/dL was 100% on days 1 and 2. From day 3, the meal changed into super-LCD with 12% of carbohydrates.

Average blood glucose was gradually reduced, which was 235 mg/dL, 202 mg/dL, 228mg/dl, on day 3,4,5, respectively. Time percentage of satisfactory blood glucose 70-180 mg/dL (/24h) was 0%, 0%, 2%, 14%, 0% from day 1 to day 5, respectively.

On Day 6, the SGLT2 inhibitor was given in the early morning. Then, the blood glucose level was acutely reduced. Average blood glucose was 169 mg/dL and 121 mg/dL on day 6 and 7. Time percentage of satisfactory blood glucose 70-180 mg/dL (/24h) from day 6 and day 7 was 54% and 100%, respectively (**Fig-1**).

On day 14, the diabetic biomarkers were remarkably improved. The value of HbA1c was 8.6%, and glycoalbumin (GA) was 22.2%.

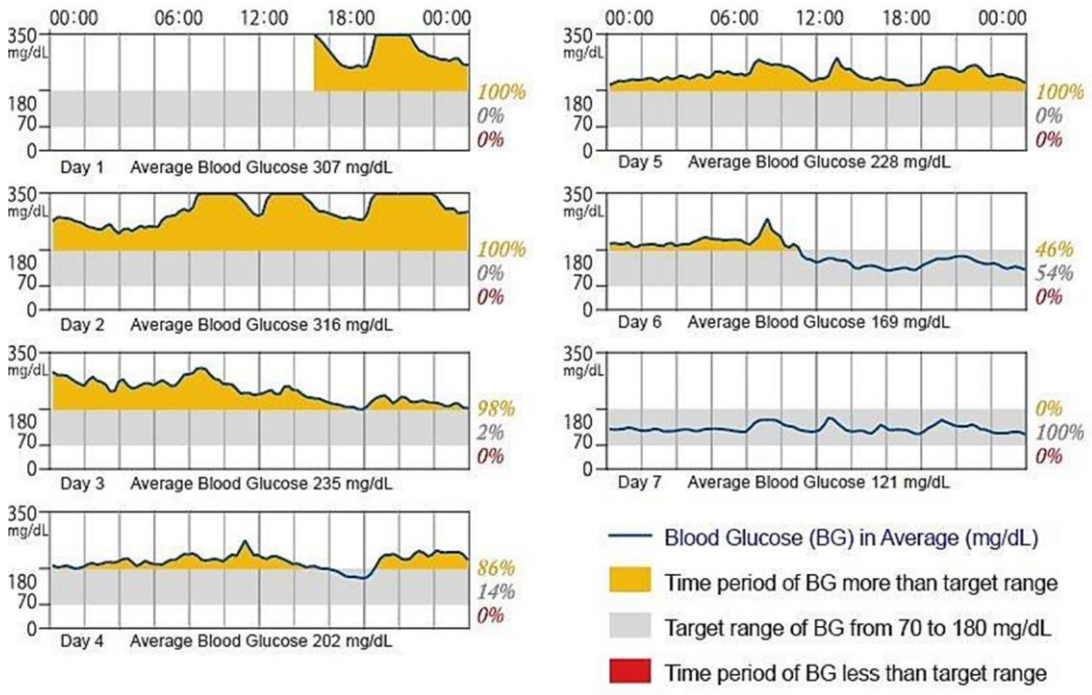

Fig-1: Daily Profile of Blood Glucose by CGM (mg/dL)

Discussion

Historically speaking, the technical aspect of CGM was formerly reported by Updike et al. [19]. After that, some CGM experimental trials concerning the electrodes were observed [20]. There was the CGM guideline by the Clinical and Laboratory Standards Institute (CLSI) [21]. In addition, international standardization was presented such as mean absolute relative deviation (MARD) and precision absolute relative difference (PARD) [21,22].

As for the clinical significance of CGM, the usefulness of the glucose variability was observed in patients with T2DM and other types [23]. Furthermore, the Food and Drug Administration (FDA) has recognized the management concerning the decisions of insulin dose from obtained CGM results [24].

CGM has been prevalent in diabetic practice as a useful apparatus in evaluating blood glucose variability and also artificial pancreas systems [25]. Successively, a real-time CGM (rtCGM) system was developed, which has been called flash glucose monitoring (FGM) [26]. Regarding the values of blood glucose, considerable agreements were observed between CGM and FGM, and then FGM has been applied to clinical practice with recent development [27]. As FGM reveals similarity to conventional CGM, there are some useful differences present in the case of FGM. One of the benefits is that the sensor has been factory calibrated without the necessity of calibration for blood glucose testing over 14-day. In addition, another benefit of FGM has been cheaper

than that of CGM [28]. On the other hand, it lacks the alarm mechanisms and connectivity in the case of continuous subcutaneous insulin infusion (CSII). Consequently, FGM has been highly evaluated to have usability and validated accuracy and usability in T1DM and T2DM [29].

In this report, we show the usability of FGM and the clinical effect of SGLT2 inhibitors have been introduced to the clinical practice, and they were proved to be a potent and effective agent for diabetes [30]. Since then, SGLT2 inhibitors have been evaluated to reveal clinical effects in various countries and then widely used [31]. Regarding their action, they inhibit renal reabsorption of glucose in the kidney. Consequently, blood sugar can be effectively reduced regardless of insulin activity [30,31].

Results of the randomized controlled trial (RCT) have been reported for the effectiveness of SGLT2 inhibitors. As a result, HbA1c, fasting blood glucose and body weight have been reduced safely and effectively [32]. There is a recent study of the post-marketing surveillance study of ipragliflozin. In this multi-center study, clinical efficacy was also confirmed [33].

In the current study, the case showed the remarkable effect of SGLT2 inhibitor [34]. The case was provided a super-LCD meal on day 3,4,5. During three days, the blood glucose was moderately reduced compared with those in day 2. After that, the SGLT2 inhibitor was administered on the morning of day 6. The profile of blood glucose showed an acute reduction from noon. This efficacy would be by the reduction of glucose toxicity that has been persisted for a long period. The definition of glucose toxicity means the impaired function of insulin secretion and sensitivity from persisting hyperglycemia [35]. SGLT2 inhibitor has several mechanisms, such as increased urinary excretion of glucose and then decreased values of glucose profile [35].

As for the measurement of urine sugar in the current case, the amount per day on day 3-5 was reduced as 47.7g, 17.2, 6.8 g/day. These data seemed to be the short-term effect of LCD. Successively, 52 g of urine sugar was observed on day 6. From these data, the SGLT2 inhibitor administration has brought the 45g difference of urinary sugar excretion between day 5 and day 6. Consequently, oral restriction of carbohydrate and urinary carbohydrate excretion would probably have a common pathophysiological mechanism.

From the pharmacological data of ipragliflozin, the amount of glucose excretion in urine was related to the renal function [34]. Daily excretion of glucose per day was reported to be about 71 g/day in normal subjects, 61g/day in rather mild renal impairment, 38 g/day in moderate chronic renal disorder and 12g/day in severe chronic renal failure [36]. Then, these data suggest that the SGLT2 inhibitor would have a similar clinical effect to LCD meal for limiting the amount of carbohydrate 70g per day.

In this case, a large amount of sugar was excreted in the urine, and then the blood glucose level was decreased. As a result, the period of high hyperglycemia was significantly reduced from day 3 to day 7. The activity of ipragliflozin is said to last 48 hours [37]. The usual dose for adults is typically 50 mg once a day and can be increased to 100 mg [38]. Based on the above, it is possible to adjust the dosing interval and dose amount depending on the situation of the patient [37].

From the pharmacological point of view, SGLT2 inhibitors excrete high levels of sugar in the urine, and adverse effects include urinary tract infections and genital infections [39]. In our current study, FGM has shown that SGLT2 inhibitors may show an acute effect on the blood glucose variability associated with the consecutive urinary sugar excretion. Consequently, our data suggest that the administration of SGLT2 inhibitors could be investigated depending on the case in clinical settings.

In summary, T2DM patient was examined in the light of blood glucose variability with three situations. Those include meal intervention of CR, LCD, and LCD with an SGLT2 inhibitor. LCD showed the clinical

efficacy of lowering blood glucose. Furthermore, a remarkable lowering glucose effect was observed just after the administration of the SGLT 2 inhibitor. Our current report could be useful data for the administration of SGLT2 inhibitor depending on each case in future diabetic therapy.

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