



## Variability Of Glucose And Lifestyle In Continuous Glucose Monitoring (CGM)

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### Abstract

**Background:** Investigation of glucose variability is crucial for patient with Type 1 Diabetes mellitus (T1DM) on insulin treatment. For Continuous Glucose Monitoring (CGM), FreeStyle Libre (Abbott) has been introduced to clinical practice with useful and beneficial efficacy.

**Case and Results:** The patient was 55 year-old T1DM female with body mass index (BMI) 21 kg/m<sup>2</sup>, HbA1c 8.0 %. She was on CGM for 14 days, with obtained glucose data in every 15 minutes. Treatment included multiple daily insulin injection (MDI) of Insulin Aspart 3 times and Insulin Glargin once a day. She showed unstable blood glucose variability with hyperglycemia and hypoglycemia, besides 2 hours delay shift in daily lifestyle rhythm. There was a discrepancy of HbA1c between actual value 8.0% and presumed value 6.9% by FreeStyle Libre.

**Discussion and Conclusion:** Obtained glucose data from FreeStyle Libre have been satisfactory. One reason for lower HbA1c value would be from the characteristic tendency in lower glucose region. Larger distribution of glucose variability would be due to delayed shift of lifestyle, sleep situation and irregular meal. These results would become the basal data for CGM, the reference to better modification of MDI and clinical diabetic practice in future research.

### Key Words:

Continuous Glucose Monitoring (CGM); FreeStyle Libre; Type 1 Diabetes Mellitus (T1DM); Mean Absolute Relative Difference (MARD); Low Carbohydrate Diet (LCD)

### Abbreviation:

Continuous Glucose Monitoring (CGM); Type 1 Diabetes Mellitus (T1DM); Mean Absolute Relative Difference (MARD); Diabetes Control and Complications Trial (DCCT); Epidemiology of Diabetes Interventions and Complications (EDIC); Low Carbohydrate Diet (LCD); Morbus (M) value; Clinical and Laboratory Standards Institute (CLSI); Subcutaneous Continuous Glucose Monitoring System (SC-CGM); Multiple Daily Insulin (MDI) Injection

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## Case Report

### Introduction

Globally, patients with diabetes mellitus have been increasing in many countries [1]. Several mega study showed the importance of controlling the blood glucose such as Diabetes Control and Complications Trial (DCCT) and Epidemiology of Diabetes Interventions and Complications (EDIC) [2,3]. Then, study of the profile of blood glucose has been crucial. Authors and colleagues have continued research about daily profile of glucose, Morbus (M) value and low carbohydrate diet (LCD) in various patients and situations [4,5,6].

On the other hand, some beneficial effect has been found in recent years that patients with T1DM show the tendency to live longer [7]. One of the reasons seems to be decreased episodes of hypoglycemia [8], and it was supported by the medical apparatus of continuous glucose monitoring (CGM) [9].

CGM has been effective for decrease the episode of hypoglycemia. The DIAMOND study (Multiple Daily Injections and Continuous Glucose Monitoring in Diabetes) which was T1DM patients treated with multiple injection therapy, showed improved HbA1c with less hypoglycemia [10]. This study was a prospective, randomized clinical trial of CGM for adults.

CGM has been developed for the beneficial therapy of diabetes mellitus, especially for T1DM. At first, the concept of CGM was reported formerly by Updike et al. [11]. After that, there was improvement of electrodes for converting blood glucose concentration into electric signals, and several trials for CGM were found [12].

Recently, the guideline for CGM was presented by the Clinical and Laboratory Standards Institute (CLSI) [13]. In succession, there have been many research about the international standardization, including precision absolute relative difference (PARD) and mean absolute relative deviation (MARD) [14,15].

In recent years, useful medical apparatus, FreeStyle Libre (Abbott, USA) has been introduced to clinical practice. It has flash

glucose-sensing technology and has been rather prevalent [9,16]. In this study, patient with T1DM is presented with some clinical problems to be explored in detail.

### Case Presentation

**History of present illness:** The subject is a female patient with type 1 diabetes mellitus (T1DM). She is 55 year-old treated with insulin therapy for 12 years. The diabetic control was formerly stable, but it is rather unstable with HbA1c around 8% during half-year. There are episodes of hyperglycemia and hypoglycemia ranging from about 40 mg/dl to 400 mg/dl.

From mentioned above, we thought the necessity of further evaluation about swinging blood glucose. Then, daily profile of blood glucose was measured by the useful apparatus, FreeStyle Libre (Abbott).

**Physicals and Routine Exams:** As basal data, her physicals were normal, such as vitals, heart, lung, abdomen and neurological findings. Her body mass index (BMI) was 21 kg/m<sup>2</sup>. Laboratory examination on routine revealed as follows: HbA1c 8.0%, glucose 356 mg/dl, Hb 13.8 g/dl, WBC 6400 / $\mu$ l, Plt 27.5 x 10<sup>4</sup>/ $\mu$ l, AST 20 IU/ml, ALT 23 IU/ml, r-GT 27 IU/ml, Alb 4.4 mg/dl, BUN 18 mg/dl, Cre 0.6mg/dl, Uric Acid 5.8 mg/dl, HDL 39 mg/dl, LDL 94 mg/dl, TG 373 mg/dl. HbA1c level was 7.4%-7.7% 6-9 months ago, and has been from 7.7% to 8.3% in last 6 months, which indicates keeping rather high HbA1c value.

**Insulin therapy:** Patient has been on the multiple daily insulin injection (MDI) by Novo rapid (Novo Nordisk) 3 times a day, and Insulin Glargine (Eli Lilly and Company) at night once a day. The former is Insulin Aspart provided by pre-filled pen including 100 units/ml, and the latter is Insulin Glargine by BS injection kit FFP including 300 units/ml. As to the clock time and insulin units are in the following: Aspart is given 21, 25, 23 units on 1000h, 1400h, 2000h and Glargine is given 11 units on 2400h.

**CGM study:** The patient had CGM in May

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2018. Daily profile of blood glucose was measured by FreeStyle Libre, and it was satisfactory without any symptoms or problems.

The results for 14 days are shown in *Fig.1*. Lifestyle of the patient seems to be about 2 hours delayed from usual lifestyle. The meal time is 1000h, 1400h, 2000h, 3 times per day. Then, the injection of insulin is given at 1000h, 1400h, 2000h, 2400h, 4 times per day. Median glucose showed rather high between 1000h and 1400h. Otherwise, median glucose level seems to be stable.

From the result of *Fig.1*, there are two points to be investigated. One is unstable variability of glucose. The distribution of blood glucose was so wide associated with hyperglycemia and hypoglycemia. The patient did not feel specific symptoms, in both episodes of hyperglycemia and hypoglycemia.

Another point is the discrepancy of HbA1c value. Presumed HbA1c value analyzed by FreeStyle Libre was 6.9%. On the other hand, HbA1c value in the outclinic at the first day of CGM study was 8.0%. There exist some discrepancies between the both values.

### Sensor-based device for CGM

The FreeStyle Libre Flash Glucose Monitoring system is the sensor-based device for blood glucose monitoring, which was produced by

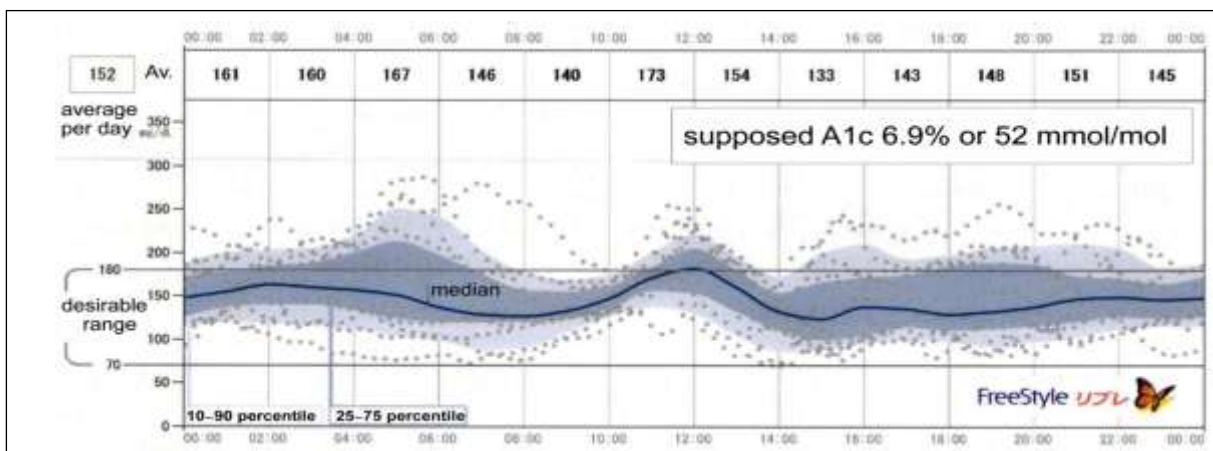
Abbott Diabetes Care Inc., Alameda, CA, USA [9].

This newly-developed system was the first commercially available medical apparatus [17]. Its beneficial point would be that factory-calibrated sensors are used [18]. When detecting for episodes of hyperglycemia and hypoglycemia, it can operate for replacing blood glucose examining and checking up trends and tracking patterns. The beneficial points are precise, convenient and small size for clinical practice [16]. The sensor is attached on the back of the arm for 2 weeks and automatically stores the data of glucose level in every 15 min [9,16].

### Discussion

The research for CGM has been continued for years in order to develop the standard care for T1DM patients [19]. In comparison with the former blood glucose monitoring (BGM), newly-developed CGM can represent 24-hour detail glycemic variability and prediction of changes on glucose at the same time. In succession, the application of CGM becomes wider for the patients with various situations [20]. Moreover, in United States, Food and Drug Administration (FDA) could approve the management decisions in 2016 including the insulin dosing from obtained CGM values [21].

FreeStyle Libre was analyzed for safety, accuracy and user acceptability using 89 T1DM children cases [16]. On the other hand,



**Fig.1 Results of Continuous glucose monitoring (CGM)**

CGM data for 14 days was obtained in May, 2018. Presumed HbA1c was 6.9% from analysis of FreeStyle Libre. On the other hand, actual HbA1c value in outclinic on the first day of this exam was 8.0%. There was a discrepancy of HbA1c value between them.

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FreeStyle Libre subcutaneous continuous glucose monitoring system (SC-CGM) showed the data that Mean difference (SD) was reported to be -43.4 (20) mg/dl [22]. In addition, there was tendency to indicate lower measured values in the lower ranges, and was also underestimation of the response of glucose rise for the meal loading [23]. It is reported that the mean absolute relative difference (MARD) of glucose levels would be 20.3%, 14.7%, 9.6% in the range of <72, 72-180, 181<, respectively [24].

These data reported before may be one of the reasons for explaining the lower value in HbA1c of our current study.

In this study, blood glucose variability of the T1DM case was investigated by CGM. Blood glucose profile for 14 days showed rather wider range of fluctuations, compared with usual and standard case. There was characteristic situation in this case with insulin treatment. Time lag and delay was found in the daily life of the patient. About 2 hours delay was present in the clock time of meal and insulin injection just before meal. As comparing the usual time with that in this case, it is 08h to 10h in the morning, 12h to 14h in the day, 18h to 20h in the evening and 22h to 24h before going to bed.

From midnight to early morning, a wide distribution of blood sugar is observed from 0200 h to 0800h. As to this phenomenon, several factors are involved in the cause. Hypoglycemia occasionally continues from midnight to early morning. In this situation, the patient has not taken anything before going to bed. Although blood glucose level is rather low, she is sleeping fast without recognizing hypoglycemic symptoms or any other symptoms. As to well-known hypoglycemic symptoms, she did not feel hunger, palpitations, sweating, tremor, fatigue, headache, dizziness, drowsiness and so on.

Conversely in 5 out of 14 days, hyperglycemia was continuing from midnight to early morning. One cause would be the following episode. When she was just preparing the injection of Lantus on the table, she was falling to sleep at once sitting on the chair. Another episode is found that she took milk and bread during lying

in the bed because of feeling hungry. In this case, blood glucose increased about 180 mg/dL. Intake amount of carbohydrate seemed to be 35-40 g. It is said that blood glucose increases 5mg/dL for carbohydrate 1g in T1DM, and then it seems to be consistent with the actual increase.

In every morning at 10 am, blood sugar always converges to the same level. Breakfast is always vegetable salad such as tomato and cabbage, and bread. There is a small fluctuation of blood glucose during 10-14h. This is probable from the different physical activity, such as housework, washing and walking around.

The afternoon meal is usually at 14 o'clock. The way to eat is vegetable first, and there are many dishes such as cabbage and fish at lunch, while carbohydrate is rare or less. At 15-20 o'clock, she always has lots of things to do associate with physical activity and exercise. As the exercise is harder, blood glucose is lower at night. For dinner, she takes vegetables, meat, fish, egg and rice about 80g including 28g of carbohydrate.

According to the recent report, there were studies about the accuracy of blood glucose monitors (BGMs). The results were that only 6 of 18 commercially available BGMs consistently met accuracy standards. Consequently, the necessity for CGM study would be increased with expectation from now [25].

### Conclusion

As regard to this study, glucose variability in T1DM case was investigated by the application of CGM using FreeStyle Libre. Because the case has delayed lifestyle rhythm, it is so beneficial and effective for better diabetic control. These obtained results would become fundamental data for clinical practice and future study in diabetic practice.

### Supplement

This study was conducted in compliance with the ethical principles of the Declaration of Helsinki. Furthermore, it was conducted with Japan's Act on the Protection of Personal Information along with the Ministerial Ordinance on Good Clinical Practice (GCP) for Drug

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(Ordinance of Ministry of Health and Welfare No. 28 of March 27, 1997). Ethical committee meeting was held including physicians, nurse, pharmacist, clinical engineer and academic experts. Informed consent and written consent were obtained from the subject.

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