# Daily improvement of glucose variability by Continuous Glucose Monitoring (CGM)

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**ABSTRACT**

Continuous Glucose Monitoring (CGM) has been recently applied in the clinical diabetic practice. Authors have continued research of glucose variability. In this study, 51 year-old female patient with Type 1 diabetes mellitus (T1DM) was investigated. She has given multiple daily insulin injection (MDI) for long and her recent daily glucose profile was unstable. After applied with FreeStyle Libre, her blood variability was improved with the average glucose from 222 mg/dL to 135 mg/dL, which was partly from her motivation for better diabetic control. Thus, CGM may become a trigger to give beneficial influence for regular lifestyle of the patients.

**Key words:** Continuous Glucose Monitoring (CGM) FreeStyle Libre, multiple daily insulin injection (MDI), Type 1 diabetes mellitus (T1DM), Japan LCD promotion association (JLCDPA)

**Abbreviation:** CGM: Continuous Glucose Monitoring, T1DM: type 1 diabetes mellitus MDI: multiple daily insulin injection, LCD: Low Carbohydrate Diet, CR: Calorie Restriction

## INTRODUCTION

Diabetes mellitus has been important disease across the world. It has been treated by adequate glycemic control, for which some diabetic standard guidelines were presented [1]. As to diabetic therapy, nutritional treatment has been the basic method and other various dietary therapies have been reported [2]. They include calorie restriction (CR) (low-fat), vegetarian, Mediterranean, moderate carbohydrate, low-carbohydrate diet (LCD), high-protein, control, low glycemic index/ glycemic load (GI/GL) and Paleolithic [2]. Among them, recent topics would be mainly LCD, CR, and Mediterranean diet and so on.

It has been almost classified into 2 types, which are Type 2 diabetes mellitus (T2DM) and Type 1 Diabetes Mellitus (T1DM). As for T2DM, recent topics include some kinds of anti-diabetic oral agents such as SGLT2 inhibitors [3-5] and nutritional treatment such as LCD [6-7]. LCD was initiated and became popular broadly in medical and health region [6-7]. LCD has been reported to show more beneficial effect than CR [8].

Concerning LCD, authors and colleagues have firstly reported LCD in Japan [9]. Furthermore, we have continued clinical practice and education concerning LCD, in which super LCD, standard LCD and petite LCD have been proposed for continuation of LCD in daily life [10]. We have reported various research about LCD, CR, M value, meal tolerance test (MMT), CGM, and others for long [11,12]. From medical social point of view, we have developing social movement of LCD through of Japan LCD promotion association (JLCDPA) [11,12].

As for T1DM, recent topics include evaluation methods such as new treatment method such as ultra-long acting insulin plus ultra-rapid insulin [13], and continuous glucose monitoring (CGM) [14]. Among them, CGM has been developed for some years, there several reports showing clinical effect of detecting hypoglycemia episodes [15]. Furthermore, beneficial CGM reveals higher self-efficacy, lower diabetes distress, simultaneous response and other positive technology points [16,17]. GM has been rather popular recently in the clinical practice [17]. It has been a sensor-based apparatus for diabetes mellitus [18]. Most well-known device has been FreeStyle Libre, that is from Abbott Diabetes Care Inc., CA, United States [18]. It has been evaluated to be reliable for long, because it is simple and useful for detecting detail fluctuation of blood variability. Furthermore, it is convenient with small size and precise data [19].

Among our various diabetic practice and research, we have reported diabetic cases so far. In this article, we describe a case with T1DM received CGM and showed the improvement of glucose variability in short period.

## CASE REPORT
**Present History:** The case was 51-year-old female patient with T1DM with about 8 years of duration. She has continued to have insulin therapy for years. The control of diabetic state has been almost fair with HbA1c 7.2-8.4% until half years ago. After that, however, her diabetic control became unstable, with the range of 61 mg/dL to 400 mg/dL. At that time, HbA1c value was increased to 9.0% 2 months ago. Consequently, diabetes staffs in charge recommended her to check the profile of blood glucose using FreeStyle Libre.

**Physical examination:** She showed unremarkable physical status, and no consciousness disorder from hyper or hypoglycemia. The vital signs were normal, and no specific diabetic neurological disorders were found. She has normal range of body mass index (BMI) around 21.0 kg/m$^2$.

**Laboratory test:** The data of the laboratory tests were as follows: The standard biochemical data were: AST 18 U/mL, ALT 21 U/mL, r-GT 23 U/mL, BUN 19 mg/dL, Cre 0.6 mg/dL, Uric Acid 5.7 mg/dL, HDL 36 mg/dL, LDL 98 mg/dL, postprandial TG 369 mg/dL, WBC 5900 /μL, RBC 4.39 x 10$^6$/μL, Hb 13.3 g/dL, Plt 27.5 x 10$^4$/μL. Data related diabetes were HbA1c 9.5%, pre-prandial glucose 146 mg/dL.

**Insulin treatment:** She has been treated for long as multiple daily insulin injection (MDI), with four times of insulin per day. She was provided 2 kinds of insulin. They are Novo rapid (Novo Nordisk) given three times per day just before three meals. Further, she was given insulin Glargine (Eli Lilly and Company) once a day at night at 2100h – 2300h. Their brand names were Insulin Aspart by pre–filled pen including 100 units/mL, and Insulin Glargine by BS injection kit FFP including 300 units/mL. Recent dose of insulin was 25, 23, 20 units of Aspart, and 16 units of Glargine.

## METHODS

The glucose variability of the case was investigated by FreeStyle Libre (Abbott, USA) [18]. Blood glucose profile was studied for 14 days. The medical apparatus FreeStyle Libre (Abbott, USA) has showed the reliability for the stable glucose data [19]. It showed stable and beneficial results such as trend accuracy, point accuracy, alarms, calibration, and the stability of the sensor, time lag and traceability [20]. It also showed the stable results along the guideline of Clinical and Laboratory Standards Institute (CLSI) [14].

## RESULTS
Using the CGM apparatus FreeStyle Libre, blood glucose profiles are shown on day 3, 6, 9 and 12 (Figure 1). The average value of blood glucose analyzed by FreeStyle Libre showed 222 mg/dL, 148 mg/dL, 140 mg/dL and 135 mg/dL, respectively. Regarding the pattern of glucose profile, each data showed different in these days. One of the common characteristic results would be the elevated tendency during 1130h – 1430h. During midnight, glucose pattern was not the same. There is an estimated HbA1c value calculated by FreeStyle Libre, which was 7.3% or 56 mmol/mol. In contrast, actual HbA1c value in the out clinic showed 7.9% or 60 mmol/mol. Both data has a discrepancy between them.

## DISCUSSION
Concerning CGM, the advantage would be obtaining the instant and correct glucose value. It can bring the improvement of variability of glucose, less episode of hypoglycemia, and better cost-effectiveness [21,22].

There are recently some guidelines for CGM application from the endocrine society [23]. For the results of summarized of RCTs, CGM could reduce the HbA1c value by 0.28%, and lessen the episode of hypoglycemia [23]. Furthermore, CGM will have the possibility of implantable variability for coming generation in the future [24,25].
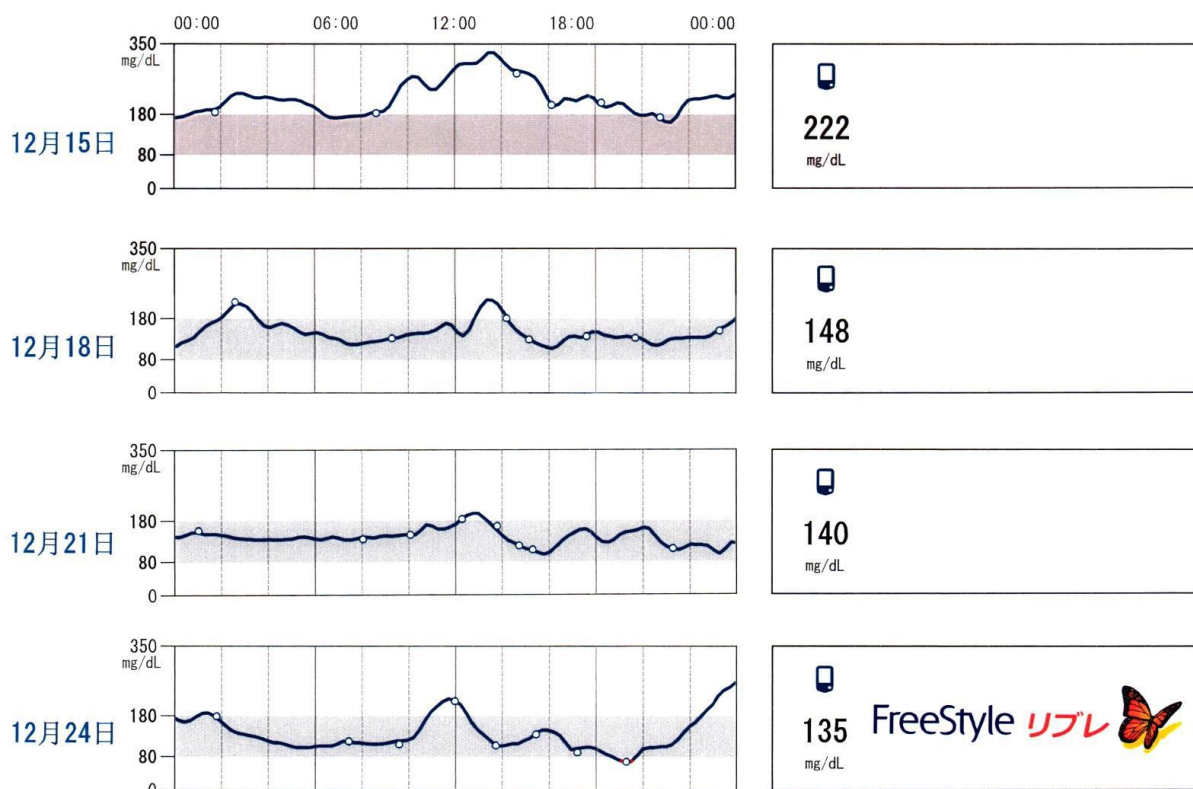


**Figure 1: Blood glucose level -(Graf:-1Day -3 Estimated HbA1c is 7.3% or 56 mmol/mol By FreeStyle Libre.); (Graf:-2, Day 6:- Measured HbA1c is 7.9% or 60 mmol/mol from out clinic data.); (Graf:-3 Day 9:- Glucose profile became in the range of 80-180 mg/dL all day long); (Graf:-4 Day 12: FreeStyle Libre)**

Along with the CGM development, adults and children with T1DM will reduce instable variability and improve glycemic control [26,27]. When T1DM case wear CGM and regulate blood glucose level adequately, the case has simultaneously large benefit of real time CGM (rtCGM) [26,28]. Consequently, diabetic therapy with rtCGM can expect ideal profile of glucose in the case of MDI [29,30]. CGM can also give more effective management of glycemic rate of change (ROC) in order to adjust the dose of insulin [31].

In this study, there was a difference of HbA1c value in 7.9% and 7.4% between out clinic and analyzed data by FreeStyle Libre. There have been similar reports found so far [32]. One reason would be that CGM cannot detect occasional abrupt increases in blood glucose [32]. In fact, blood glucose levels are measured every 7.5 min to 15 min in FreeStyle Libre and FreeStyle Libre Pro [33]. This problem will be further investigated from various points of view.

According to the previous report, FreeStyle Libre showed safety, accuracy and acceptability for pediatric patients with T1DM [19]. In contrast, mean difference (SD) of FreeStyle Libre was -43.4 (SD 20) mg/dL, which was rather large [34]. Moreover, as the value was in lower range, the glucose rise after meal was underestimated [32]. The glucose value of mean absolute relative difference (MARD) was 20.3%, 14.7%, 9.6%, respectively for the three ranges of glucose (<72, 72-180, 181<) [33].

In this study, the case with T1DM showed unstable glucose variability some months ago. At that time, it was suggested that she had irregular lifestyle [17]. After that, her daily schedule would become rather improved with less unstableness. It seems to be beneficial for her to check real time blood glucose, when wearing FreeStuye Libre for 2 weeks [35]. According to the guideline of CGM in 2019, there are recommendations for reduction of hypoglycemia, which revealed the evidence level as rank A [1].

The reason of her unstable lifestyle was evaluated with patients herself and medical staffs. She has worked as part time job with rather unstable working shift. When she was in bad diabetic control, her daily schedule was influenced to much extent. After that, she has decided her mind to keep regular hours, especially wake up, meals and sleep time. Consequently, her regular life has been kept with the trigger of CGM in FreeStyle Libre.

In summary, CGM was applied to the patient with T1DM, and detail glucose variability was investigated. Using FreeStyle Libre, her average glucose was reduced from 222 mg/dL to 135 mg/dL with her motivation for better diabetic control. Thus, CGM may become a trigger to give beneficial influence for regular lifestyle of the patients. Current report would be expected to be some reference for clinical practice.

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