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Remarkable Improvement of Glucose Variability by Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors using Continuous Glucose Monitoring (CGM)

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Abstract

Authors have continued clinical research of Calorie Restriction (CR) and Low Carbohydrate Diet (LCD) and present a case with precise observation of continuous glucose monitoring (CGM). The patient is 38 years-old females with type 2 diabetes mellitus (T2DM), who showed BMI 19.6, postprandial blood glucose 277 mg/dL. HbA1c 12.6%, glycoalbumin 31.8% (11.6-16.4), HOMA-R 2.8, HOMA-β 8.5, urinary excretion of C-peptide 67 μg/day, and normal range of liver, renal, lipid exams. She was given three stage intervention. The protocol was

- Day 1-2; CR meal with 60% carbohydrate,
- Day 3-5; LCD meal with 12% carbohydrate,
- Day 6-13; LCD+Sodium–glucose cotransporter 2(SGLT2) inhibitors (Suglat 50 mg, Ipragliflozin L-Proline).

The glucose variability was monitored using FreeStyle Libre Pro (Abbott) for 14 days. Blood glucose was decreased as

- More than 350 mg/dL,
- 180-200 mg/dL,
- 100-150 mg/dL in day 7-9, and 90-120 mg/dL in day 10-13.

Acute decrease of blood glucose was found 3 hours after giving Suglat, which was remarkable finding. These results suggest the improving glucose variability of LCD in short term, the acute and strong efficacy of SGLT2 inhibitors for glucose metabolism, and clinical usefulness of simultaneous observation of glucose fluctuation.

Keywords: Sodium–glucose cotransporter 2 inhibitors; Continuous glucose monitoring; Freestyle libre pro; Ipragliflozin L-proline; Glucose variability; Low carbohydrate diet

Abbreviations: LCD: Low Carbohydrate Diet; T2DM: Type 2 Diabetes Mellitus; CR: Calorie Restriction; HOMA-R: Homeostasis Model Assessment of Insulin Resistance; HOMA-β: Homeostasis Model Assessment of β cell function; NCD: Non-Communicable Diseases; ACP: American College of Physicians; ADA: American Diabetes Association; DIRECT: Dietary Intervention Randomized Controlled Trial; JLCDPA: Japan LCD Promotion Association; MTT: Meal Tolerance Test; FGM: Flash Glucose Monitoring; CGM: Continuous Glucose Monitoring; IGI: Insulinogenic Index; SGLT2: Sodium–Glucose Cotransporter 2; 75gOGTT: 75 g Oral Glucose Tolerance Test; IRI: Immunoreactive Insulin; RCTs: Randomized Controlled Trials; BMI: Body Mass Index.

Introduction

Historically speaking, various health problems and diseases were threats to humans in each era. In the past, infectious diseases such as tuberculosis had been raging, but at present non-communicable diseases (NCD) has been important. Among them, diabetes mellitus and metabolic syndrome have become major problems medically and economically [1]. This influence is spreading to the world in the developed countries, as well as developing countries [2]. The principle for the therapy is an appropriate diet, and medicine can be given if necessary. As to the adequate diagnosis and treatment of diabetes, several medical academies have been on discussion [3]. Recent controversies are found for recommended HbA1c value in some societies, such as American College of Physicians (ACP), and American Diabetes Association (ADA) [4,5].

Under such circumstances, calorie restriction (CR) was previously broadly prevalent for standard diet therapy for long. After that, Atkins and others advocated the trial of Low Carbohydrate Diet (LCD), which

was spreading in the European and North American countries [6]. Furthermore, lots of evidence for LCD has been accumulated until now and the efficacy of LCD has been reported. In particular, Dietary Intervention Randomized Controlled Trial (DIRECT) Group clarified the clinical effects of LCD until 2 years and also until 4 years [7,8]. After that, there are several reports indicating the clinical usefulness of LCD [9,10].

On the other hand, the authors firstly introduced LCD and started in Japan [11]. After that, we have continued published many books and developed educational seminars in order to inform people of correct information of LCD and nutritional therapy. In addition, we established Japan LCD Promotion Association (JLCDPA) for the purpose of proceeds the movement from social point of view. Through these activities, we have expanded various activities concerning LCD for the patients, healthcare professionals and general people.

For our research development related to LCD, we are continuing various aspects of investigation. They include

- The popularization of three types of LCDs that can be applied on a daily basis, which are petit LCD, standard LCD and super LCD [12],
- The concentration of blood ketone bodies increased in response to LCD continuation, as well as physiological hyperketonemia in the axis of fetus, placenta, newborn and mother [13],
- Glucose variability and daily profile of blood glucose on CR and LCD [14],
- Meal tolerance test (MTT) using CR breakfast with carbohydrate 70 g [15].

In recent years, the development of medical technology for blood glucose measurement has been found. Then, investigation of blood glucose variability has become possible with detail observation. As a matter of fact, flash glucose monitoring (FGM) and continuous glucose monitoring (CGM) systems have been introduced in the medical practice. Consequently, the analysis of detail glucose fluctuation can be measured easier than before. We have had lots of diabetic cases with the study of CGM. Among them, we have recently experienced an interesting case with type 2 diabetes (T2DM). When she was switched from CR to LCD, blood glucose variability rapidly improved remarkably in the short term. Furthermore, providing SGLT2 inhibitor cause blood glucose decreasing in a few hours. We analyzed this case in detail, and report in this article.

Case Presentation

Patient and history

The patient is 38 years-old female with T2DM. History of present illness revealed that she was diagnosed as T2DM at the age of 26. After that, she had been treated by anti-diabetic oral agents. However, her diabetic control has not been satisfactory for long. Then, she was introduced and transferred to our diabetic clinic for further evaluation and treatment.

Physicals and routine exams

On first contact, her physical was normal, such as vitals, heart, lung, abdomen and neurological findings. She was 164 cm in height and 52.7 kg in weight, with 19.6 kg/m^2 of body mass index (BMI).

Laboratory examination on routine revealed as follows

Postprandial blood glucose 277 mg/dL. HbA1c 12.6%, glycoalbumin 31.8% (11.6-16.4). Three weeks later, she was admitted for detail evaluation and practical and actual therapy for current diabetic condition. At this point, HbA1c was 11.2%, and glycoalbumin was 26.4%.

General examination

Urinalysis showed that pH 6.0, protein negative, sugar 1892 mg/dL, urinary microalbumin 6.5 mg/g･cre (<30). Occult blood in stool was negative. ECG was within normal limit. Echograms of carotid artery, heart and abdomen were unremarkable.

Blood biochemistry

The results of blood test were as follows. CBC (complete blood count): WBC 4100/μl, RBC 492 × 10^4/μl, Hb 13.1 g/dL, Ht 39.9%, CRP 0.03 mg/dL, Na 138 mEq/L, K 4.6 mEq/L, Cl 101 mEq/L, BUN 13 mg/dL, Cre 0.51 mg/dL, Uric Acid 4.1 mg/dL, Ca 9.5 mg/dL, P 3.4 mg/dL, Total protein 7.1 g/dL, Albumin 4.2 g/dL, AlP 242 IU/mL, GOT 16 IU/mL, GPT 16 IU/mL, LDH 162 IU/mL, r-GTP 15 IU/mL, ChE 324 U/L (200-459), Amylase 74 U/L (37-125), Triglyceride 53 mg/dL, HDL-C 81 mg/dL, LDL-C 138 mg/dL, Cystatine C 0.60 mg/L (0.56-0.87).

Diabetes-related exam

On the morning of day 2, fasting blood glucose and IRI was 254 mg/dL and 4.5 μU/mL. Homeostasis model assessment of insulin resistance (HOMA-R) was 2.8 and homeostasis model assessment of β cell function (HOMA-β) was 8.5. In addition, glucose and IRI on 30 minutes after CR breakfast was 317 mg/dL and 14.0 IU/mL, respectively. The carbohydrate content in the breakfast is 70 g, in which 1400 kcal per day and 60% of carbohydrate for 3 meals. Insulinogenic index (IGI) for 70 g of carbohydrate per os is calculated as (14.0-4.5)/(317–254)=0.15. Urinary excretion of C-peptide on day 2 and day 4 was 67.0 μg/day and 55.2 μg/day, respectively.

Methods and Clinical Progress

Protocol of three intervention

This study includes the following three steps:

- CR was provided in day 1 and 2. The detail of CR is 1400 kcal/day with 60% of carbohydrate.
- LCD was provided from day 3 to 5. The detail of LCD is 1400 kcal/day with 12% of carbohydrate, which is called super-LCD in our research protocol.
- Oral medicine was added on day 6 to 13. Anti-diabetic agent of Sodium–glucose cotransporter 2 (SGLT2) inhibitors (Suglat 50 mg, Ipragliflozin L-Proline) was started on the morning of day 6. The meal is as same as LCD and continued from day 6 to 13.

Method of CGM study

Daily profile of blood glucose was measured by FreeStyle Libre Pro. As to products, there are two types of Freestyle Libre [16]. One is Personal CGM, FreeStyle Libre, and another is Professional CGM,

FreeStyle Libre Pro. The latter apparatus was used in this study, which is produced by Abbott Diabetes Care Inc. [17,18].

Result of CGM

The results for 13 days are shown in Figure 1. The meal time is regular and stable at 0800h, 1200h and 1800h, 3 times per day. After three meals, blood glucose levels were increased in postprandial periods.

For day 1-2 with 60% of carbohydrate on CR meal, daily blood glucose persisted high level. The portion of glucose 350 mg/dL means actually more than 350 mg/dL, because of upper limit of the system is 350 mg/dL and less than 350 mg/dL.

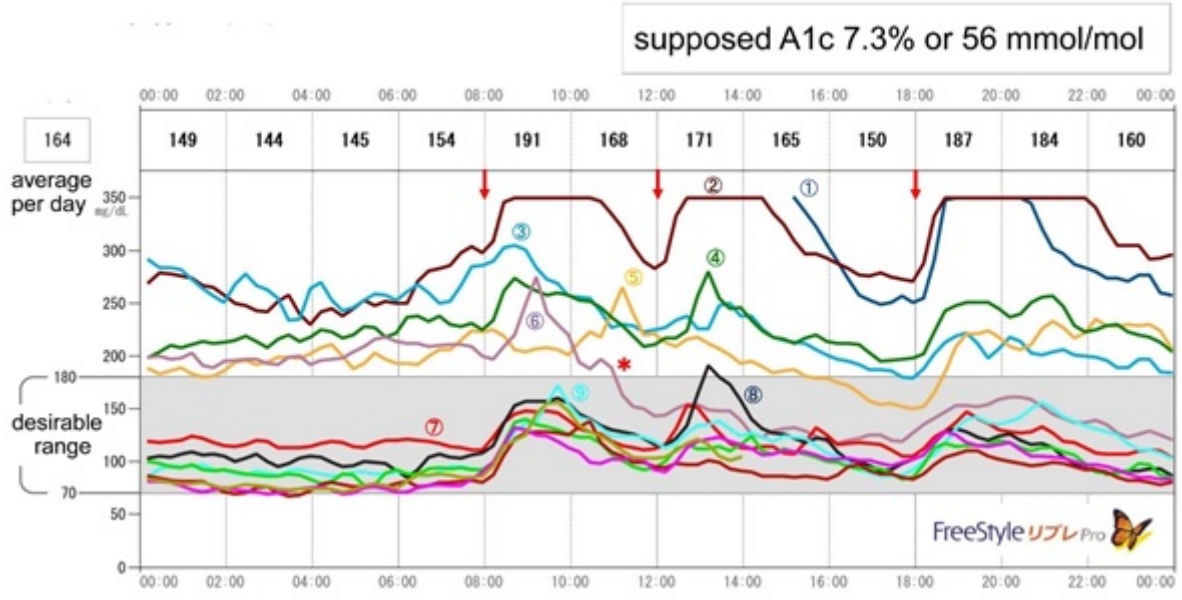

Figure 1: CGM data for 3 intervention study in patient with T2DM. CR meal in day 1-2. LCD meal in day 3-5. LCD + SGLT2 inhibitor day 6-9. Red arrows indicate 3 meals per day. Asterisk (*) shows the point of clinical effect of SGLT2 inhibitor on day 6.

During day 3-5, blood glucose was decreased rather acutely than day 1-2. The decrease degree would be about 150 mg/dL, and the average blood glucose on day 3-5 was approximately 180 mg/dL to 200 mg/dL. When blood variability was compared between day 3 and day 5, the latter showed more decreased blood glucose level than the former. On the afternoon of day 5, blood glucose was decreased to the level less than 180 mg/dL.

On the morning at 0800h of day 6, anti-diabetic agent of SGLT2 inhibitors (Suglat 50 mg, Ipragliflozin L-Proline) was started. It was continued from day 6 to day 13. Three hours after the initiation of SGLT2 inhibitor, blood glucose has abruptly decreased to around 120 mg/dL to 150 mg/dL and persisted after that. On day 7-9, blood glucose maintained about 100 mg/dL to 150 mg/dL. On day 10-13, glucose maintained from 90 mg/dl to 120 mg/dL in the daytime, and 70 mg/dL to 90 mg/dL in the night, in particular rather lower from 0100h to 0600h.

Discussion and Conclusion

In this report, a patient with T2DM received three stages of treatment. These are i) CR meal, ii) LCD meal, and iii) LCD+SGLT 2 inhibitor, and blood glucose variability was investigated using recently developed FreeStyle Libre Pro (Abbott). As a result, hyperglycemia continued on day 1

-2 on CR. After that, blood glucose level dropped daily at day 3-6, indicating the short-term effect of LCD. Furthermore, by the administration of SGLT 2 inhibitor agent, blood glucose was dramatically decreased, suggesting a rapid and high efficacy of the agent.

From the clinical application of FreeStyle Libre Pro, it seems to be simple, useful and informative. There are not particular problems of measurement data or equipment worn on arms, and so on [16].

As a matter of fact, the discrepancy of the data would be examined. In other words, there was a data divergence between HbA1c measured at hospitalization and HbA1c anticipated by FreeStyle Libre Pro from blood glucose data. The reason for this would be partly attributed to the fact that CGM cannot detect occasional acute and spike increase of the blood glucose [19]. One of the reasons would be blood measurement is done in every 15 minutes as reported in the past [20]. Similar situation was observed in our previous report. From now on, accumulation of data will be expected to solve this problem.

This case showed the HOMA-R value elevated to 2.8. In general, it is judged that HOMA-R shows normal under 1.6, and insulin resistance more than 2.5. Then, this case has obvious insulin resistance for long history of diabetes [21].

Further, HOMA-β was 8.5. As to the interpretation for the value HOMA-β, 40-100% is normal, 30% or less is a mild secretory capacity reduction, 15% or less means a clearly reduced insulin secretion ability, and 3% or less means that the insulin ability is regarded as the level of exhaustion. Consequently, the case was evaluated to be obvious secretion reduction [22].

As mentioned above for this case, continuation of hyperglycemia for many years probably induced the existence of a vicious circle due to sugar toxicity. Therefore, it seems that both insulin resistance and insulin secretion ability where was also decreased to the moderate degree. However, a short period of providing LCD meal has reduced the sugar toxicity and therefore the clinical significance of LCD would be effective and meaningful.

A method for evaluating insulin secretion from the pancreas has been known so far. It is IGI for the examination of 75 g oral glucose tolerance test (75gOGTT), which can be calculated with glucose and immunoreactive insulin (IRI) at 0 and 30 minutes.

Similarly, the authors have been studying the responses of blood glucose and IRI in response to LCD and/or CR meals so far. Among them, MTT trials using CR breakfast has been reported [15]. CR breakfast includes 70 g of carbohydrate, and IGI was examined like 75gOGTT. As a result, it seems that IGI-carbo 70 is actually useful in the clinical diabetic practice and research [15].

In current case, the blood glucose increased from 254 mg/dL to 317 mg / dL after 30 minutes due to ingestion of 70 g carbohydrate, and the ratio of IGI-Carbo 70 was calculated to be 0.15. Compared with the conventional IGI-75 g-glucose, the insulin secretion ability was clinically shown to be decreased.

In recent years, SGLT2 inhibitors have been used. They are one of the new oral anti-hyperglycemic agents, which seem to show remarkable effect for glucose variability [23,24]. Their mechanism includes the inhibition of renal reabsorption of glucose and promotion of glycosuria, which can lead to a reduction of blood glucose independent from insulin activity [24,25].

The administration of ipragliflozin once per day has safe and effective decrease of HbA1c, fasting blood glucose and body weight in randomized controlled trials (RCTs) [26]. Its beneficial effects were also recognized in post-marketing surveillance study [27].

In this case, the effect of SGLT 2 inhibitor was remarkably observed. The agent was administered at 0800 h on day 6. After that, blood glucose has dropped sharply from 1100h. It is involved in the mechanism of action of SGLT2 inhibitor [28]. This is probably from the reduced situation of "glucose toxicity" which were persisted by long-term hyperglycemia. Glucose toxicity has been known where chronic hyperglycemia directly impairs both insulin secretion and sensitivity [29]. SGLT2 inhibitors have an insulin-independent mechanism of action, which involves increasing urinary glucose excretion and decreasing blood glucose [29].

Pharmacological research data of ipragliflozin showed Cmax 1045 ng/mL, Tmax 1.43 hrs, and t 1/2, 14.9 hrs. Clinical effects are seen about 3 hours, and administration once a day is usual [28,30].

Other data showed that glucose excretion in urine is 71 g/day in average for normal subjects, 61 g/day for mild renal disorder, 38 g/day for moderate renal disorder, and 12 g/day for severe renal disorder. In other words, it can be interpreted that it is close to continuing the carbohydrate limit of 70 g per day. When limiting carbohydrate intake by dietary restriction and discharging 70 g of sugar per day with SGLT 2 inhibitor, both has common situation in sugar metabolism with doubling clinical effects [28,30].

As for ipragliflozin, usual dosage for adult is 50 mg orally administered once daily before or after breakfast. This dose can be increased up to 100 mg with careful monitoring of the clinical progress of the patient if needed [31]. The inhibitory effects of ipragliflozin on SGLT2 and SGLT1 were studied in human SGLT2- or SGLT1-expressing CHO cells. As a result, IC50 values were 7.38 and 1880 nmol/L, respectively [31]. SGLT2 inhibitors have maintaining activity for 48 h, and then we can arrange to give the patient as-required single doses instead of daily administration [32]. It can be helpful for the therapy of T2DM to reduce the adverse effects such as urinary tract infection, genital infection, hypoglycemia and so on [33].

In summary, we examined the detailed blood glucose fluctuation by CGM in a patient with T2DM, associated with 3 interventions of CR meal, LCD meal, LCD+SGLT 2 inhibitor. Blood glucose variability was improved with LCD meal for 1-2 days, and was dramatically improved 3 hours after the administration of SGLT 2 inhibitor. Thus, hyperglycemia and glucose toxicity seemed to be reduced in short period. These data would become basic and reference data and be useful for future CR and LCD diet therapy and actual administration of SGLT2 inhibitor.

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