



Normalized glucose variability by Low Carbohydrate Diet (LCD) in CGM study

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Abstract

In diabetic practice, **continuous glucose monitoring** (CGM) has been more used for glucose variability. Authors have reported and developed the clinical study of **Low Carbohydrate Diet** (LCD) and **Calorie Restriction** (CR) through **Japan LCD Promotion Association** (JLCDPA). A diabetic case is presented with normalizing glucose variability by LCD meal checked by CGM. Case is 51 years female with type 2 diabetes mellitus (T2DM). At first visit, HbA1c was 10.0%, glucose was 288mg/dL, BMI 39.1, GOT 16IU/mL, HDL-C 33mg/dL, Triglyceride 152mg/dL. CR meal was provided on day-1 to day-5 and LCD meal with 12% carbohydrate on day-6 to day-13. Average glucose value from CGM was 292mg/dL, 235mg/dL, 160mg/dL, 140mg/dL, 124mg/dL in day 3,5,7,9,11 respectively. On day-13, total Ketone bodies (T-KB) 540 μ mol/L (-131), Acetoacetic acid (AcAc) 86 μ mol/L (-55) and 3-hydroxybutyric acid (3-OHBA) 454 μ mol/L (-85). Weight reduction was 5kg on day-14 and 11.2kg on day-70 with BMI 34.6. Thus, LCD showed a remarkable glucose-lowering effect in short term. FreeStyle Libre (Abbott, USA) seems to be a useful apparatus for monitoring the detailed fluctuation of blood glucose. These results would become fundamental and reference data and contribute to the LCD research development in the future.

Keywords:

3-Hydroxybutyric Acid (3-OHBA); Ketone Bodies; Continuous Glucose Monitoring (CGM); Japan LCD Promotion Association (JLCDPA); FreeStyle Libre

Abbreviation:

LCD: Low Carbohydrate Diet; T2DM: Type 2 Diabetes Mellitus; CR: Calorie Restriction; JLCDPA: Japan LCD Promotion Association; AcAc: Acetoacetic acid; 3-OHBA: 3-Hydroxybutyric Acid

Introduction

Medical problems concerning diabetes, obesity and metabolic syndrome have been crucial and necessary to manage in many countries worldwide [1]. Adequate nutritional treatment is the fundamental therapy for those

health problems [2]. **Calorie restriction** (CR) meal is formerly one of the standard therapy. After that, **low carbohydrate diet** (LCD) has been introduced to the medical and health field and was initiated by Atkins and Bernstein [3,4]. Successively, LCD has been prevalent and

developed widely until now.

After that, the medical evidence of LCD was reported by investigators [5]. They include **Dietary Intervention Randomized Controlled Trial (DIRECT)** Group presenting LCD efficacy until 2 and 4 years [5, 6]. The definition of LCD includes a rather wider area, and various levels of LCD has been tried and reported for years [7]. Furthermore, large scale studies concerning the clinical effect of LCD was presented, such as **NIPPON DATA80** (National Integrated Project for Prospective Observation of Non-communicable Disease and Its Trends in the Aged 1980) Research Group and the **Prospective Urban Rural Epidemiology (PURE)** study [8,9].

Associated with the research development of LCD, there have been some changes to the guidelines in several international diabetic societies. One of the controversies would be the recommended HbA1c value, concerning what degree of strict control of glucose variability would be necessary [10,11]. Research development of LCD will contribute to the discussion in the future because LCD improves the average of blood glucose and **Mean Amplitude of Glycemic Excursions (MAGE)**.

On the other hand, LCD in Japan was firstly introduced by Ebe, one of the authors [12]. After that, LCD has been gradually developed for diabetic patients. Furthermore, the author reported the important relationship among LCD, pregnant women, diabetes and ketone bodies [13]. In other words, a remarkably high level of blood ketone bodies were observed in pregnant women, neonates, placenta, and fetuses, and the various physiological roles of ketone bodies were reported [14].

The author has continued treating many cases with gestational diabetic cases with LCD [13,14]. Through our clinical treatment and research, there was a new case with type 2 diabetes mellitus (T2DM). Daily profile of blood glucose in the case was studied by continuous glucose monitoring (CGM), and it was remarkably improved by LCD meal for several

days. The details of the case would be analyzed and reported in this article.

Case Summary

Present History:

The subject was 51 years old female. As past history, she has hypertension and allergic state for pollen allergy. She developed fatigue, sweating, frequent urination, feeling irritability and dizziness for some weeks. Then she thought the possibility of the climacteric syndrome in herself and she came to our clinic.

Urgent examination for diabetes showed that blood glucose was 288mg/dL and HbA1c was 10.0%. She was diagnosed as type 2 diabetes mellitus (T2DM).

Examination:

Physical examination showed in the following. Consciousness and vitals were normal. Lung, heart, abdomen and neurological were unremarkable. Her physique was stature 160cm, weight 100kg and body mass index (BMI) was 39.1kg/m².

Chest X-ray and Electrocardiogram (ECG) were normal. Urinalysis showed positive for glucose, negative for protein.

Blood biochemistry tests were as follows: GOT 16 U/L, GPT 20U/L, total protein 7.1g/dL, BUN 15mg/dL, Cre 0.6mg/dL, T-Cho 195mg/dL, HDL-C 33mg/dL, Triglyceride 152mg/dL, Fe 74µg/dL, UIBC 237µg/dL (110-425), complete blood count; RBC 498 x 10⁴/µl, Hb 15.9g/dL, WBC 7,600/µl. Others were unremarkable.

Research Protocol

In this study, the daily profile of blood glucose was investigated. For measurement of detail fluctuation of blood glucose, FreeStyle Libre [15] was applied for 2 weeks [16]. This medical apparatus is used for Continuous Glucose Monitoring (CGM) [17]. After many years of research, it has been made and delivered by Abbott Diabetes Care in several countries [15].

For long years, authors have continued clinical research about LCD and CR. There has been a certain clinical study protocol for the meal of LCD and CR. CR includes the balance of three macronutrients with PFC ratio is 15:25:60. This is the standard ratio of the recommended meal from Japan diabetes Association (JDA) [18].

In contrast, LCD meal was selected 12% of carbohydrate in calorie ratio, which has been called as **super-LCD**. Its definition was made and prevalent by Dr. Ebe et al. in Japan LCD Promotion Association (JLCDPA).

In this study, the subject was provided with the standard formula meal according to our research protocol. The schedule is as follows:

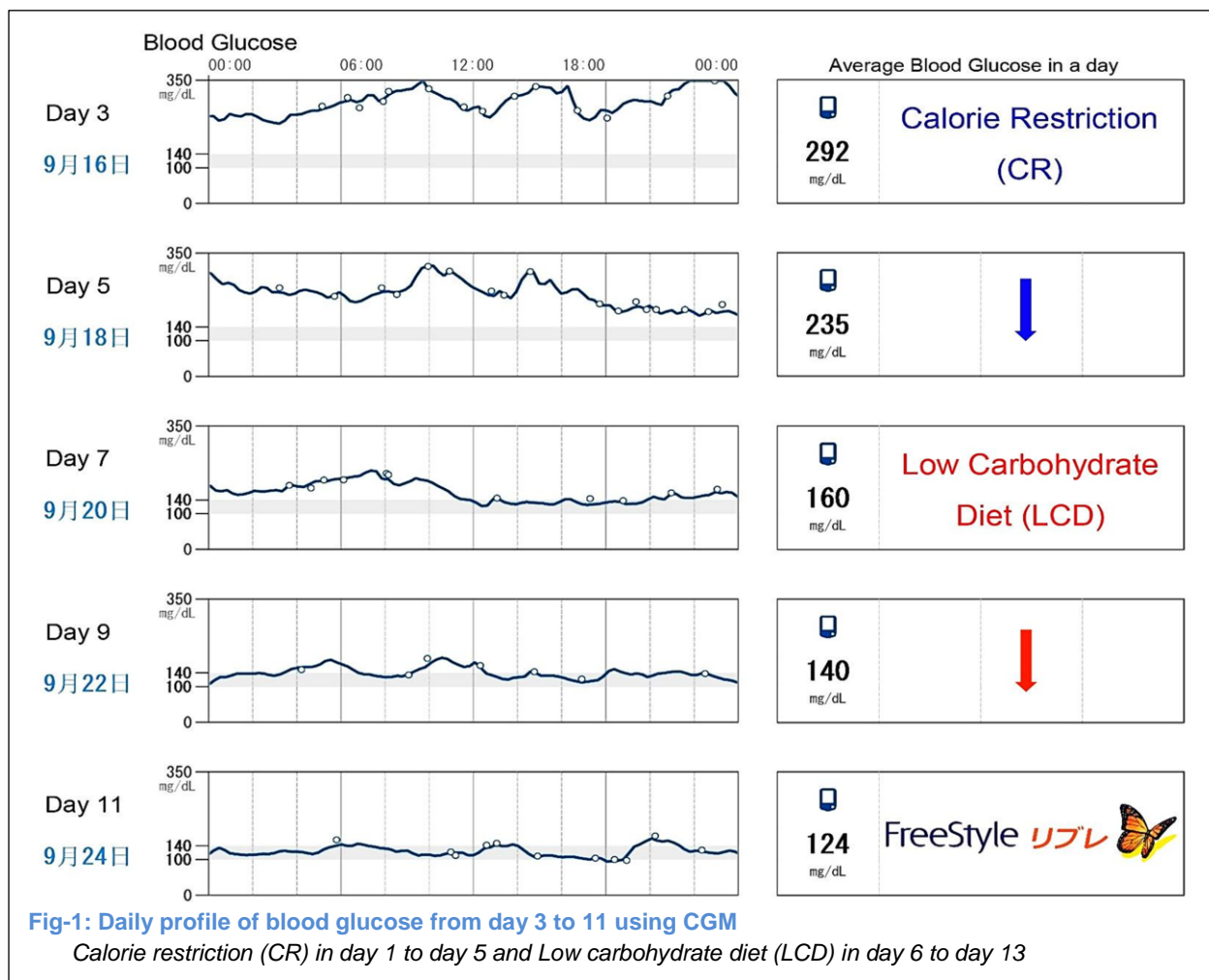
- I. The subject was given CR meal from day-1 to day-5, including 60% of

carbohydrate which is standard meal in Japan as per Japan Diabetes Association [18].

- II. The clock time of three meals was at 0800, 1200, 1800h, respectively in regular schedule.
- III. The subject was given super-LCD meal from day-6 to day-13, including 12% of carbohydrate.
- IV. Detail glucose variability in 24 hours a day was continued from day-1 to day-13.

Course and Results

Using the FreeStyle Libre, the result of CGM for a daily profile of blood glucose was shown in **Fig-1**. Formula meal of CR was given from day-1 to day-5. The average blood glucose per day was 292mg/dL on day-3, and 235mg/dL on day-5, in which the average data was decreasing.



On the other hand, formula meal of LCD was given from day-6 to day-13. The average blood glucose per day was 160mg/dL on day-7, 140mg/dL on day-9, 124mg/dL on day-11, respectively. This data showed a remarkable decrease in five days. On day-11, the daily profile of blood glucose showed almost normal range. Furthermore, the fluctuation between preprandial and postprandial blood glucose has been decreasing gradually and remarkably.

Blood values for ketone bodies on day-13 were measured, in which total ketone bodies 540 μ mol/L (-131), Acetoacetic acid (AcAc) 86 μ mol/L (-55), 3-hydroxybutyric acid (3-OHBA) 454 μ mol/L (-85). All fragments of ketone bodies were elevated.

Until day-14, there were remarkable changes in the sign and symptom. Body weight was decreased to 5kgs and pretibial edema (PTE) was remarkably reduced until day-21. She felt the decrease of fatigue, hunger sensation, and stressful mood because of no limitation for eating meat and egg. Furthermore, she felt stable psychologically with the decreased opportunity to scold her children, indicating that her irritability was remarkably relieved. Her body weight was decreased to 88.8kg with BMI 34.6kg/m² in day-70, indicating clinical efficacy of LCD.

Discussion and Conclusion

With regard to LCD, Dr. Ebe started to apply LCD to diabetic patients in Japan, and developed LCD in Japan. He has established Japan LCD Promotion Association (JLCDPA) and we have continued to give general people correct and useful information of LCD through lots of occasions such as seminars, books, and reports in medical societies for years [19]. Simultaneously, LCD often brings elevated hyperketonemia. The physiological role of ketone bodies is extremely important in clinical practice. In the axis of a fetus-placenta-newborn-pregnant mother, KB can produce necessary energy instead of glucose [19].

In this study, blood levels of ketone bodies were measured for 7 days after starting to give

LCD meal to the subject. As a result, blood values of T-KB, AcAc, and 3-OHBA were elevated. The level of 3-OHBA which has the main function of the ketone body was 5 times higher than the standard value in this study.

The effects of ketone bodies (KB) has been gradually known with lots of beneficial function in metabolic and other axes in man [20,21]. They are

- I. Elevated KB in blood is not the risky situation
- II. Brain and muscle can use KB similar to glucose
- III. KB generate much energy
- IV. KB has anti-cancer effects [22].

Glucose intake 20-40g per day will cause elevation of 3-OHBA of approximately 1 mM (1000 μ mol/L) with wide variations [23, 24].

In the diabetic patients provided with LCD meal, blood values of total ketone bodies showed 160 to 4,000 μ mol/L (0.16 to 4 mmol/L) [25]. From this data, current total KB and 3-OHBA would be in the range as expected.

In the history of diabetes care, recently introduced CGM has given a big impact [26]. Among them, FreeStyle Libre (Abbott, USA) has been a useful apparatus for CGM with a sensor-based method for glucose monitoring [27]. With CGM, the frequency of hypoglycemia in type 1 diabetes was reduced [28]. Furthermore, blood glucose fluctuation could be revealed in type 2 diabetes [29].

Practical data on CGM has been accumulated for long years. **Clinical and Laboratory Standards Institute** (CLSI) announced the CGM guidelines [30]. Furthermore, international standardization has continued the researches on the precision absolute relative difference (PARD) and mean absolute relative deviation (MARD) [31, 32].

From the current data on day-3, the blood glucose has risen from 230mg/dL to

350mg/dL, and the difference between preprandial and postprandial glucose is 120mg/dL. In the case of T2DM, blood glucose is said to increase by 3mg/dL per 1g carbohydrate intake. Therefore, it is presumed that about 40g of carbohydrate was ingested. On the other hand, on day-11, there is almost no difference between preprandial and postprandial glucose value. This seems to be related to decreased carbohydrate intake by LCD, increased insulin secretion response and decreased insulin resistance.

In summary, blood glucose decline was found in the patient with T2DM in a short period by LCD. The difference between preprandial and postprandial glucose, mean glucose and MAGE were decreased. Further, weight reduction was shown 11.2kgs in 10 weeks. These results suggest the increase of insulin secretion and a decrease of insulin resistance by the effect of LCD in a short period, with the useful data of a clinical application of LCD for future research.

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