

Improved Glucose Variability of Continuous Glucose Monitoring (CGM) By Intake of Japanese Healthy Tofu as Low Carbohydrate Diet (LCD)

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Abstract

Background: Concerning Type 2 Diabetes (T2D), some recent clinical trends have been found such as evaluation method by continuous glucose monitoring (CGM) and nutritional therapy by low carbohydrate diet (LCD).

Case presentation: The case is 66-year-old men with T2D for 24 years duration. His diabetic control had been stable, but HbA1c was elevated to 8.1% in January 2022. He was advised to take Japanese healthy tofu instead of rice as LCD, and received CGM for totally 6 weeks. [Results] His daily profile of blood glucose was improved, and HbA1c decreased as 6.9%, 6.4%, 5.9% by estimated HbA1c calculated by FreeStyle Libre.

Discussion & conclusion: For actual LCD continuation, Morinaga silky tofu showed clinical effects. However, some discrepancy of HbA1c values between estimated HbA1c by CGM and out-clinic HbA1c by laboratory test would be present. Possible reasons include i) detection of glucose in every 7.5-15.0 min, ii) glucose level in the interstitial tissue. Such accumulated research data would be hopefully reference for future development.

Keywords: Type 2 Diabetes (T2D); continuous glucose monitoring (CGM); low carbohydrate diet (LCD); FreeStyle Libre; Morinaga silky tofu

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Introduction

Type 2 Diabetes (T2D) has been managed for crucial disease across the world [1]. It may influence to broad area from social and medical points of view [2]. In Jan 2022, American Diabetes Association (ADA) has announced the latest guideline for diabetic medical care [3]. Recent development includes further detail evaluation for the fluctuation of blood glucose [4]. Among them, continuous glucose monitoring (CGM) has been gradually well-known examination for medical diabetic practice [5]. CGM includes two kinds of real-time CGM (rtCGM) and intermittently scanned CGM (isCGM). Lots of investigations concerning CGM have been found, which showed beneficial and useful clinical efficacy. By applying CGM, patient and physician can grasp current glucose data for adequate therapy [6]. Further, rtCGM can provide information of probable high and low glucose values which requires rapid intervention of carbohydrate per os or insulin administration [7].

Aiming for better blood glucose variability by CGM, lower intake of carbohydrate amount would be required. From nutritional treatment point of view, Calorie restriction (CR) had been

formerly the standard method for diabetic patients. After that, low carbohydrate diet (LCD) has been introduced to medical practice and also health care area by some doctors of Bernstein and Atkins [8,9]. Clinical effectiveness was found by some trials, such as Dietary Intervention Randomized Controlled Trial (DIRECT) study [10]. Thus, LCD has been evaluated to show beneficial efficacy with several degrees of LCD [11]. In contrast, authors and medical collaborators have started clinically LCD practice in Japan [12]. We established Japan LCD Promotion Association (JLCDPA), and developed LCD movement broadly [13]. For further enlightening of LCD, three LCD types were socially introduced, which are super-LCD, standard-LCD and petite-LCD [14]. We have also reported clinically effects of improving obesity by continuing LCD, in which >10% weight reduction was achieved for 25% in thousands of obesity cases [15].

As mentioned above, our clinic practice and research fields include diabetes, CGM, chronic kidney disease (CKD), non-communicable diseases (NCDs) and related diseases [16-18]. Among various actual clinical cases, we have experienced an impressive male case with T2D. He showed improved glucose variability by CGM associated with continuing LCD. In this article, general clinical progress of the

case will be described.

Current medical history

The case is a 66-year-old man. He had no particular illness when he was young. He weighed 68 kg at the age of 20 and had a maximum weight of 85 kg at the age of 42. At that time, he was diagnosed as T2D with fatigue, polydipsia, polyuria, and weight loss. Family history showed that both of his parents were diabetic. Regarding diabetic treatment, he has been treated with oral hypoglycemic agents (OHAs) since then. Insulin treatment has been started from 60 years, and he has been generally stable until now about HbA1c 7.0%. However, HbA1c was increased to 8.1% in Jan 2022. Looking back on his daily life for a few months, diet and exercise situation was somewhat inadequate. Recent treatment is summarized as follows. Oral medicine included Valsartan (80) 1Tab, Rosuvastatin (2.5) 1Tab and Ipragliflozin L-proline (50) 1 Tab in the morning. Insulin therapy included Insulin Degludec (Genetical Recombination) 8 units in the evening, and NovoRapid Injection FlexTouch 8-8-8 units 3 times a day.

Physical Examination

The case had unremarkable findings of physical examination, or no remarkable abnormalities of vitals, consciousness and speech. His stature showed height 173.5cm, body weight 77.6kg, body mass index (BMI) 25.8 kg/m². He showed negative findings of lung, heart, abdomen and neurological examination. Concerning

retinopathy, he has occasionally complained of slightly blurred vision, and he was pointed out to show pre-proliferative diabetic retinopathy for some years. He has not felt remarkable neurological motor and sensory abnormalities. He was explained to have some nephropathy for years, in which eGFR showed about 47-50 mL/min/1.73m².

Laboratory Exam

The results of fundamental laboratory examinations in Jan 2022 were shown in the following. General biochemical data were AST 17 U/mL, ALT 19 U/mL, r-GTP 28 U/mL, Uric Acid 5.8 mg/dL, BUN 22 mg/dL, Cre 1.21 mg/dL, eGFR 47.3 mL/min/1.73m², HDL 58 mg/dL, LDL 111 mg/dL, TG 134 mg/dL, WBC 5700 / μ L, RBC 5.17 x 10⁶/ μ L, Hb 15.6 g/dL, Plt 17.9 x 10⁴/ μ L. Data related diabetes were HbA1c 8.1%, pre-prandial glucose 96 mg/dL.

Clinical progress

For conducting further evaluation and adequate treatment, his daily profile of blood glucose was investigated by CGM method using FreeStyle Libre (Abott). This apparatus can monitor simultaneous glucose changes in detail for every 15 minutes during 2 weeks. His glucose variability was shown for 6 weeks (Figure 1). His actual blood glucose fluctuation has become remarkably improved for this period. According to the calculation by the computer built-in the FreeStyle Libre, estimated HbA1c was decreased from 6.9%, 6.5% and 5.9% for 6 weeks.

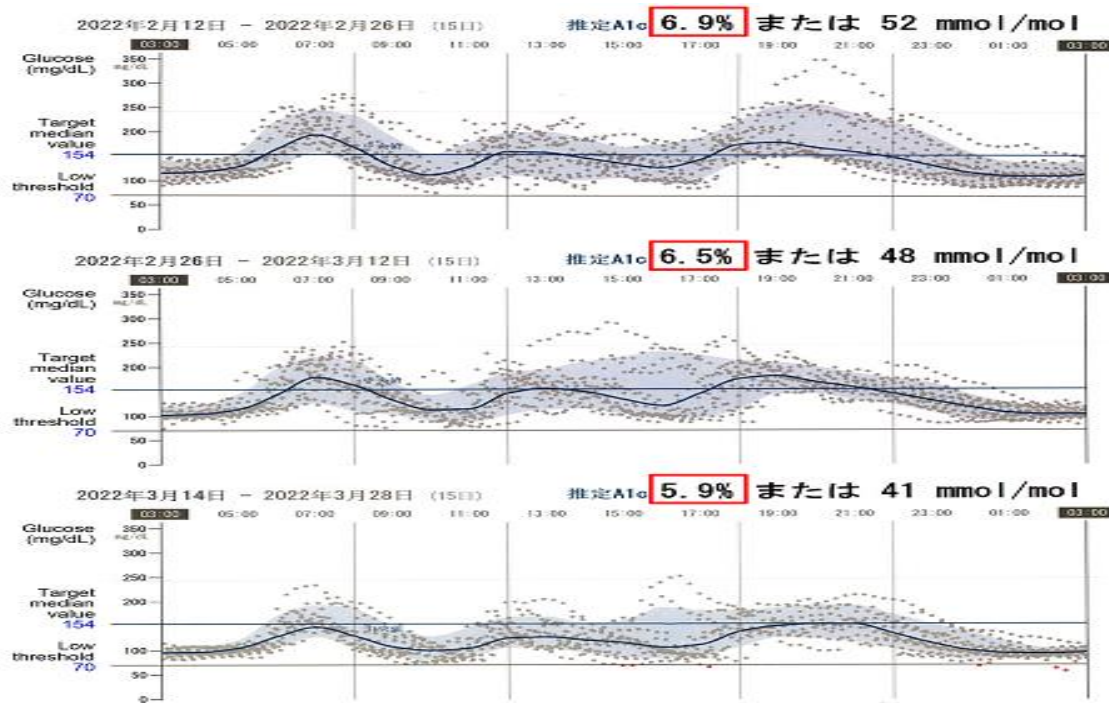


Figure 1: Blood glucose profile by CGM using FreeStyle Libre for 6 weeks.

However, the consecutive HbA1c values in the out-clinic were different from those by Libre. The data were 8.0% on Feb 10, and 7.8% on Mar 14. Moderate discrepancy was present between out-clinic HbA1c value by laboratory exam and estimated HbA1c value calculated by FreeStyle Libre (Abott). During this period, he energetically continued adequate diet and exercise therapy to

improve his diabetic condition as much as possible. Among them, he has reduced the amount of rice, bread and noodles as possible, which are made of carbohydrate. Instead of these foodstuffs, he has tried to take “Japanese healthy silky Tofu” which includes less carbohydrate and more protein (Figure 2).



Figure 2: Japanese healthy tofu with less carbohydrate suitable for LCD.

- a) Blue-color tofu: regular silk tofu, with 250g weight, carbohydrate 2.9g /100g.
- b) Brown-color tofu: protein-plus tofu, with 253g weight carbohydrate 2.7g/100g.

Ethical Considerations

The present report has been fundamentally performed according to the ethically former principles of Helsinki Declaration. In addition, several comments were along with the Ethical Guidelines for Human Research. It was basically associated with Good Clinical Practice (GCP). Related to current study, authors and co-researchers established the ethical committee for arguing adequate considerations. The committee was set within the hospital which includes some professional persons. They include the president, physician, nurse, pharmacist, nutritionist, and also the personnel of legal specialty. We have fully discussed various matters with adequate manner and conclude the agreements for current protocol. The document of informed consent was provided from the patient in charge.

Discussion

In current case report, some medical and clinical aspects would be discussed. They include i) continuous glucose monitoring (CGM), ii) adequate diet therapy from his experience and iii) actual nutritional situation consuming Japanese healthy tofu for last three months. Three aspects of discussion would be described

in this order.

In order to investigate detail fluctuation of blood glucose, the case received the examination of CGM by using FreeStyle Libre [19]. It was firstly introduced to medical practice for CGM with factory-calibrated sensors [20]. It can analyze daily profile of glucose every 15 minutes for 15 days, and it is famous for stable reliability for changing in the blood glucose [21]. Among similar apparatus for measuring blood glucose, FreeStyle Libre shows beneficial predominance such as sensor stability, point accuracy, trend accuracy, alarms, calibration and traceability [22]. In addition, it can provide satisfactory results in the light of Clinical and Laboratory Standards Institute (CLSI) [23].

For the current data, there were moderate discrepancy between actual measurement value of HbA1c in the out-clinic and estimated HbA1c by FreeStyle Libre. Such situation has been often reported for years [24]. One reason may be due to the measuring mechanism, in which CGM is difficult to catch up acutely increasing blood glucose. Successive glucose levels are detected in every 7.5-15.0 min by two representative devices of FreeStyle Libre Pro and FreeStyle Libre [25]. Another reason may be from the fact that it can detect glucose level not in the blood vessel, but in the interstitial tissue. Thus,

estimated HbA1c by Freestyle Libre may become one reference data of changing glucose level.

From recent report, comparative data (n=641) were analyzed concerning estimated HbA1c and laboratory HbA1c [26]. The protocol included T1D cases (91%), diabetes history (more than 20 years) and CGM duration (24.5 days). The results showed that discordance of HbA1c was <0.1% in 11% cases, ≥0.5% in 50% cases and ≥1% in 22%. In particular, larger discordance was observed in cases with advanced CKD cases associated with decreased value of eGFR (<60 mL/min/1.73m²).

This case seemed to show satisfactory diet and exercise treatment from Jan to Apr 2022. As a result, the progress values of blood glucose and HbA1c revealed improvement. His body weight decreased from 77.6 kg to 73.0 kg, and the abdominal circumference also decreased. As a matter of fact, the case continued some useful and beneficial tips for better diabetic situation in the light of diet and exercise.

As regards to his actual nutritional aspect, the following behaviors were observed. i) As the major change, the staple food was changed from rice to tofu [27]. ii) Eat three meals regularly on 0600h, 1100h and 1800h without snacks. iii) After 2000h, refrain from eating any food without just water. iv) For breakfast, reduce rice as possible when eating Japanese style [28]. v) Drink milk at first just before taking breakfast. vi) After that, eat raw vegetables, especially tomato. vii) Always have tofu instead of rice for each meal. viii) Try to avoid food containing high calories as possible. ix) Change snack content from chocolate to nuts and beans [29].

Appropriate exercise has been performed as shown below. i) Playing golf is his hobby, and it seems to be adequate level of exercise intensity. ii) He played golf in the golf course about 5 times a month. iii) He often tried to clean his garden and mow the grass regularly. iv) These kinds of exercise would be physically and psychologically appropriate.

This diabetic case has changed the content of the meal from rice to Japanese tofu. Concerning the amount of carbohydrate, rice 300g includes carbohydrate 108g, whereas tofu 300g includes carbohydrate 6g. According to the Harper's biochemistry textbook, T2D case may elevate blood glucose 3mg/dL by carbohydrate intake 1g [30]. Then, intake of tofu in daily life would be beneficial for continuing LCD. As Japanese traditional food, tofu has been fermented product which is made of soybeans [27]. Its content has approximately 35-45% of protein and 18-26% of lipids associated with less carbohydrate. From research of tofu, soybean quality of high/low protein (44.8%/39.1%) and with/without 11x globulin polypeptide was studied [31]. As a result, soybeans with high protein showed smaller seeds producing firmer tofu gels and creamier color. Another report for arteriosclerosis and tofu consumption is found [32]. For 652 Japanese men, relationship of brachial-ankle pulse wave velocity (baPWV), soyfood intake and fermented soy products were

investigated. The results showed that larger consumption brought less arterial stiffness, indicating isoflavone effect.

Concerning Japanese healthy tofu, there are various beneficial effects from medial, nutritional and social points of view. The Morinaga Silky Tofu is the preserved food which is classified in filled tofu with possible preservation period of 216 days from the date of manufacture [33]. From historical and social points of view, it has long process of development. They are i) success of preservation without preservative in 1977, ii) Awards from Ministry of Science and Technology, Japan in 1978 for aseptic tofu manufacturing method in container, iii) Japan gift promotion award 2015, and iv) Japan antarctic research expedition 2020 brought this to Japan antarctic base. The characteristic point includes the beneficial paper pack. It actually has a 6-layer structure, and its inside is coated with aluminum foil. This blocks light and oxygen, prevents quality deterioration, and enhances storage stability. Two types of tofu have been prevalent widely (Figure 2). They are a) Blue-color tofu: regular silky tofu. A block has 250g weight with protein 5.7g, fat 3.6g, carbohydrate 2.9g, 67 kcal/100g, and b) Brown-color tofu: protein-plus tofu. A block has 253g weight with protein 6.2g, fat 3.1g, carbohydrate 2.7g, 64 kcal/100g [33].

There are some limitations in this report. It is only one case report, which cannot generalize all situations and events. By continuing LCD and taking tofu, the case showed improved glucose variability by CGM. However, all nutritional taken carbohydrate amount could not be calculated. Then, the detail relationships among decreased blood glucose, HbA1c and carbohydrate amount cannot be clarified.

In summary, 66-year-old male with T2D showed improved glucose variability of CGM by continuing LCD and tofu intake. This impressive case would hopefully provide meaningful diabetic treatment and research in the future.

Conflict of interest

The authors declare no conflict of interest.

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