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PUBTEXTO

Honeymoon Phase by the effect of Low Carbohydrate Diet (LCD) after onset of Type I Diabetes (T1D)

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Abstract

The case is a 68-year-old female with Type 1 diabetes (T1D). She had an unremarkable history until 2017, and developed elevated HbA1c 7.5% in Nov 2018 with positive glutamic acid decarboxylase Antibody (GADA) 154 U/mL. Consequently, she was diagnosed as T1D and daily profile of blood glucose was studied by continuous glucose monitoring (CGM). For calorie restriction diet (CRD) days 1-2, and super-low carbohydrate diet (LCD) days 3-14, time in range (TIR) was increased from 82% to 100%. LCD prolonged the honeymoon phase for 16 months without insulin administration. After that, insulin degludec 2 units/day was initiated from Mar 2021.

Keywords: Glutamic Acid Decarboxylase Antibody (GADA); Continuous Glucose Monitoring (CGM); Low Carbohydrate Diet (LCD); Time in Range (TIR); Honeymoon Phase

Introduction

From historical and medical points of view, diabetes has become a crucial disease across the world. For nutritional treatment, a calorie restriction diet (CRD) was formerly applied, and after that low carbohydrate diet (LCD) has been recently prevalent. Various studies for LCD have been reported, and clinical effects have been known for weight reduction, decrease of HbA1c value, improvement of fatty liver and so on [1]. Further, LCD contributes to drop in triglyceride (TG), low-density lipoprotein (LDL) and blood pressure, and elevation of high-density lipoprotein (HDL) [2]. Thus, its efficacy leads to reduction of insulin resistance, HbA1c and blood glucose variability for Type 2 diabetes mellitus (T2DM) [3].

On the other hand, patients with type 1 diabetes mellitus (T1D) also have clinical effects from LCD [4]. Post-prandial blood glucose will be elevated acutely in T1DM patients [5]. In many studies, LCD effects on T1DM has been beneficial for HbA1c reduction, glycemic variability and mean amplitude of glycemic excursions (MAGE), improved time in range (TIR) and lipid profile [6]. Thus, LCD continuation for T1D may bring instant effects of lower blood glucose and beneficial efficacy for a long time. Some supportive multidisciplinary approaches will be expected associated with greater diet research and supervision [4].

Patients with T1D requires insulin treatment after onset of T1D. Among them, some cases may be necessary for smaller doses shortly after initiating insulin therapy [7]. This situation is commonly referred to the honeymoon phase or remission. In most cases, it is a rather partial status where the term partial clinical remission (PCR) has been used. This mechanism is involved in the maintenance of the function of remaining beta cells. Recently, some studies clarified that adequate therapy and follow-up on the clinical progress during the honeymoon phase possibly enable the prolongation of the honeymoon phase [8]. Generally, T1D cases enter the PCR phase about 3 months after initiating insulin treatment, and this phase would persist for approximately 6-9 months. Thus, several metabolic and clinical factors are involved in the analyses for the duration and remission rate of the honeymoon phase.

Authors and collaborators have initiated LCD at first in Japan and developed LCD clinically and socioeconomically [9]. We established the Japan LCD promotion association (JLCDPA) and enlightened numerous people about adequate and useful methods. They are super-LCD, standard-LCD and petite-LCD that includes carbohydrate in calorie ratio as 12%, 26% and 40%, respectively [10]. We have reported various reports on LCD practice and research for T2D, T1D, SPIDDM, LADA and so on [11,12]. During our practice and research, we recently experienced a meaningful T1D female patient with a longer honeymoon phase by continued LCD. Her medical course and related perspectives will be presented in this article.

Case Presentation

Medical History

Current case is a 68-year-old female with T1D. She has a previous history of cervical cancer with complete hysterectomy, childhood asthma, acute cholangitis and reflux esophagitis (RE) but no pertinent family history. She managed RE symptoms

with LCD for five years leading to her T1DM diagnosis. HbA1c and fasting blood glucose (FBG) values were normal in 2016 and 2017 on annual health check reports. However, HbA1c and FBG were acutely elevated in late 2018. Further workup revealed glutamic acid decarboxylase Antibody (GADA) to be 154 U/mL (normal limit <5), and then she was diagnosed with T1D in November 2018. IRI value at diagnosis was 4.1μU/mL, indicating maintained endogenous insulin production.

In early 2019, the patient was admitted to Takao Hospital for further evaluation and treatment. She received both meals of CRD and LCD, associated with continuous glucose monitoring (CGM). She was not provided any oral hypoglycemic agents (OHAs) or injections. In day 1 and 2, she was provided 1400kcal CRD meals recommended by the Japan Diabetes Society (JDS). During day 3 to 14, she was provided isocaloric super LCD meals that contains 12% of carbohydrate. For its detailed calculation, 1400 kcal/day x 0.12 = 168 kcal/day, and 168 kcal divided by 4 kcal/g (carbohydrate) equals to 42g of carbohydrate per day.

Several exams

As a result of CGM, time in range (TIR; 70-180 mg/dL) for days 1 and 2 was 82% and 89%, respectively (Figure 1). After that, TIR was gradually increased from days 3-5. For 14 days, TIR increased from 82% to 100%, and time above range (TAR) decreased from 18% to 0%.

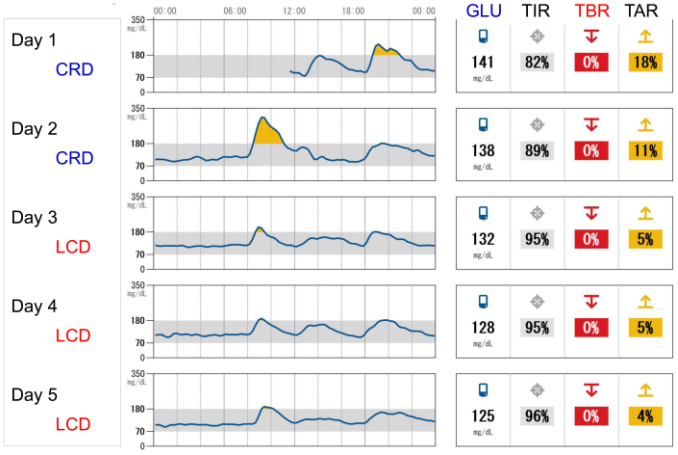

Figure 1: *The results of CGM for CR and LCD*
Daily meal was CR for day 1-2 and LCD for day 3-14.
The exam was Feb 2019, just after T1D onset.
TIR increased from 82% to 100%, and TAR decreased from 18% to 0%.

The results of biochemistry in Dec 2018 were as follows: HbA1c 7.5%, glycoalbumin 17.5%, BG 162 mg/dL, TG 77mg/dL, HDL 114 mg/dL, LDL 121 mg/dL and Cre 0.68 mg/dL. TIR showed 100% on day 8 until completion on day 14. The value of 24-hour urinary C-peptide excretion was 48.0 and 41.8 μg/day on days 3 and 4, respectively, which is lower limit normal.

Clinical progress

When she had taken CRD meal, her RE symptoms returned. Because of abdominal discomfort, she could not tolerate primarily carbohydrate-containing foods, such as rice. Following the initiation of super LCD on day 3, RE symptoms were alleviated. Despite taking no RE medications, such as proton pump inhibitors (PPIs), the patient has remained symptom-free with dietary intervention alone. No diabetes medications were prescribed at discharge. The patient's HbA1c and FBG remained stable until around the end of 2019, in which IRI was 1.4 μU/mL in November 2019, which was slightly decreased from the previous measurement.

A mutual decision was made to initiate Tresiba 2U once daily in March 2020, which provided adequate glycemic control. Insulin units have gradually been titrated up and the current dosage of Tresiba is 6-7U daily. The last CPR value was 0.3 ng/mL in January 2022, indicating continuing endogenous insulin production. The patient was 50 kg at diagnosis with weight stabilizing to around 44-46 kg (BMI 17.2 - 18.0 kg/m^2) throughout the clinical course. No elevation in creatinine or decline in kidney function markers was noted. The results of CGM in November 2020 are shown in Figure 2, in which the daily profile of blood glucose showed stable.

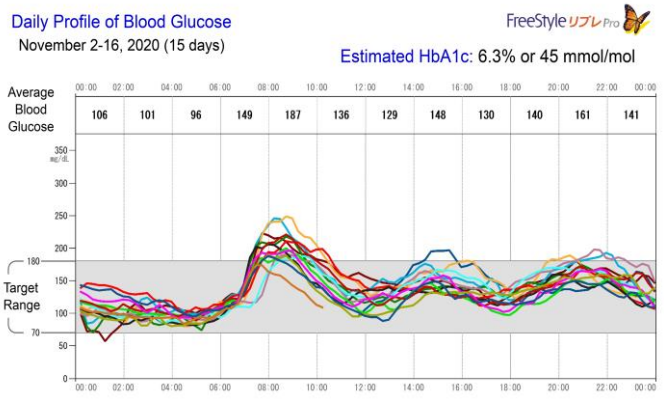

Figure 2: *The results of CGM in Nov 2020*
The exam was conducted during stable period.
Three peaks are observed from 3 meals per day.

Changes in laboratory results and treatment by insulin administration are summarized in Table 1. It shows the data from 2016 to 2023, and the type and amount of insulin used. The case has been using insulin degludec (genetical recombination), a long-acting soluble insulin analogue injection (brand name Tresiba®) [13]. The case received no insulin injections during the first few years. Afterwards a small dose of degludec was initiated and the dose has been slowly increased until now (Table 1).

Table 1: *Changes in laboratory results and insulin treatment.*

Time		Glucose variability			Endogeneous insulin			Treat	Lipids profile		
Year/Mo		HbA1c	GA	SBG	IRI	CPR	U-CPR	Unit	TG	HDL	LDL
2016	12	5.4		85				0	44	110	107
2017	11	5.6		93				0	54	116	104
2018	11	7.2		150	4.1			0	86	108	123
	12	7.5	17.5	162				0	77	114	121
2019	3	6.7	14.7	124			48	0	52	108	116
	11	7.0	16.2	149	1.4			0	45	111	114
2020	3	7.0	14.2	155				2	77	104	116
2021	2	6.9	16.6	136		0.4		3	48	109	149
	7	7.1	17.1	126				4	45	103	103
2022	1	7.1	14.8	107		0.3		6	61	109	145
	6	6.9	14.9	114				7	64	102	121
	11	7.1	18.0	127				7	52	108	112
2023	3	6.9	16.8	139				7	62	100	120
	9	7.1	19.1	113				7	61	99	125

Ethical considerations

Current patient was complied with the standard ethical guideline for Helsinki Declaration. Moreover, certain comment was found for personal information. The related principle is present in ethical rule for medical research and practice. These guidelines have been on the regulation from Japanese government. It has included Ministry of Health, Labor and Welfare and Ministry of Education, Culture, Sports, Science Technology. The author's et al. established the ethical committee concerning the case. It is present in Takao Hospital, Kyoto, Japan. This committee contains some clinical staffs, such as hospital president, physician majoring in diabetes, nurse pharmacist, dietitian, laboratory staff as well as legal professional personnel. These committee members have discussed in the satisfactory manner. The informed consent document was provided from the current case by the written data.

Discussion

This case has several unique characteristics, which can be summarized into four aspects as follows. They are 1) The patient had been on LCD for some time due to childhood asthma and reflux esophagitis (RE), 2) After the onset of T1D, the honeymoon phase continued due to the effect of super-LCD, and insulin therapy was not required for several years, 3) CGM results revealed CRD and LCD differences, and 4) the lipid characteristics were high HDL and low TG/HDL-C ratio. The discussion is presented below in this order.

First, LCD has been known for its various benefits on clinical symptoms. They include relieved allergic symptoms in dermatitis, hay fever, bronchial asthma, gastrointestinal discomfort/disturbance and so on. These improvements are from decreased intake amount of carbohydrate. LCD also has various efficacy from elevated ketone bodies (KB) in the blood. KB shows clinical effects for neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD) [14]. Furthermore, KB has treatment potential for cardiovascular diseases and cancer. KB metabolism would bring dysregulation for tumorigenesis in several types of cancer [15].

Second, due to the effects of super-LCD, the honeymoon phase is prolonged and insulin therapy was not required for several years. When this patient developed T1D, her weight was 50 kg, his BMI was 19.56, and she was thin. During the subsequent course, the patient weighed 44–46 kg and had a BMI of 17.2–18.0. Research for the honeymoon phase has been observed. Partial clinical remission (PCR) was investigated in 159 T1D subjects [16]. Cases with higher BMI at the onset showed a shorter period of PCR than the average cases. In addition, other findings revealed that i) younger age onset may predict possible comorbidity of Celiac disease, ii) female case and lower HCO3 value at onset of T1D may predict less PCR period. Another study was found for PCR status in T1D onset, in which two groups were compared between PCR (+) and PCR (-) [17]. The protocol included the measurement of several markers, such as HbA1c, glycemic target-adjusted HbA1C (GTAA1C), insulin dose-adjusted hemoglobin A1C (IDAA1C) and actual result of glucose monitoring from 189 cases with newly onset T1D.

Third, this case received 14 days' CGM exam with CRD in 1-2 days and LCD in 3-14 days, in which TIR changed from 82% to 100% and TAR 18% to 0%. Thus, CGM showed quite useful data for instant changes in detailed blood glucose variability. The Guidelines for blood sugar control using CGM was announced in 2019, and the target range was defined as 70-

180mg/dL, which is called time in range (TIR) [18]. Furthermore, TAR (time above range) and TBR (time below range) were defined as >180 mg/dL and <70 mg/dL, respectively. In usual clinical practice for T1D and T2D, TIR is indicated for >70% as a target value. TIR is approximately 70% when HbA1c is 7% [19,20]. TIR has been known to correlate with average blood glucose values, but its correlation is weak for lower glucose range [21]. Thus, TIR differs fundamentally from previous diabetic markers such as HbA1c and glycoalbumin.

Recently glycemic risk index (GRI) has been introduced as a novel composite CGM metric [22]. It provides a larger emphasis on hypoglycemia rather than hyperglycemia [23]. The optimal duration for CGM was studied with GRI investigation [24]. The protocol included continuous 90 days in maximum. As a result, 14 days sampling seemed to be adequate, and 7 days of CGM can estimate proper GRI to monitor glycemic changes. Out of T1D patients (n=202), an association of GRI and other metrics was studied by intermittent scanning continuous glucose monitoring (is CGM) [25]. As a result, GRI showed the highest correlation with TIR, and a high correlation with hypoglycemia, hyperglycemia, HbA1c, and other factors.

Fourth, this case has high HDL values probably from genetic characteristics as well as stable LDL values after LCD for years. Her lipid profile at onset of T1D showed TG 44 mg/dL, HDL 110mg/dL and LDL 107 mg/dL. Genetic findings have been identified in variants of familial hypercholesterolemia, where LDL-altering variants include APOE and ABCG8, and HDL-altering variants include ABCA1 and CETP [26]. HDL has been evaluated as a crucial role in atherosclerosis and possible positive effect in ASCVD therapy [27]. Regarding lipid panel concerns, patients on LCD will have a decrease, increase, or no change in LDL value [28]. An LDL-centered model has been known for predicting ASCVD risk [29]. In addition, TG to HDL ratio has been an important metabolic index, and TG/HDL > 3.5 is associated with insulin resistance and a greater risk of cardiovascular disease (CVD) [30]. The odds ratio for myocardial infarction regarding high compared to low TG/HDL-C ratio is 3.0 [31].

Certain limitations may exist in the article. The current case applied LCD for Reflux Esophagitis (RE) before T1D development. LCD seemed to be effective for glucose variability, but other factors may be involved in stable clinical progress, such as maintained beta cell function, lipid profile, slender physique and others.

In summary, the current case is an impressive female case, who has some characteristic features associated with the honeymoon phase. She has had stable diabetic variability for years, and the clinical progress will be followed carefully in the future.

Conflict of interest: The authors declare no conflict of interest.

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