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# Prolonged Honeymoon Period in Type I Diabetes (T1D) Patients on Low-Carbohydrate Diet (LCD)

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## Abstract

The presented case is a 68-year-old female with Type 1 diabetes (T1D). She was admitted for an emergency case with acute distress in January 2018 and was diagnosed with T1D with a blood glucose (BG) level of 459 mg/dL, HbA1c of 13.7%, glutamic acid decarboxylase autoantibody (GADA) level >2000 U/mL (<5 U/mL), and C-reactive protein (CRP) level of 1.10 ng/mL. She received Multiple Daily Injections (MDI) of insulin for 3 months, and then her HbA1c decreased to 7.3%. After that, she has been on a super-low carbohydrate diet (LCD) and received only Lantus XR and ipragliflozin. Serum CRP showed 0.2 ng/mL, suggesting a prolonged honeymoon period for years through continuous LCD.

## Keywords

Honeymoon Period, Type 1 Diabetes, Glutamic Acid Decarboxylase Autoantibody, Super-Low Carbohydrate Diet, Japan LCD Promotion Association

## Abbreviations

T1D: Type 1 Diabetes; GADA - Glutamic Acid Decarboxylase Autoantibody; LCD: Super-Low Carbohydrate Diet; JLCDPA - Japan LCD Promotion Association

## Introduction

In recent years, the treatment of diabetes has become an important issue. In January 2023, the American Diabetes Association (ADA) announced the standard treatment guidelines [1]. Among these recommendations, appropriate diet, oral hypoglycemic agents (OHAs), and insulin administration methods have been advised [2]. Historically, diabetics were once treated by restricting carbohydrate intake [3]. This was considered safe and effective until the discovery of insulin in 1921, after which Elliot Joslin, founder of the Joslin Diabetes Center, began using insulin in 1921/1922 [4]. Since then, several different methods of dietary therapy have been introduced. These include the Calorie Restriction Diet (CRD) and Low Carbohydrate Diet (LCD). Since the end of the 20th century, two physicians, Atkins and Bernstein, have advocated for the LCD [5]. Its effectiveness has been prevalent in Europe and the United States.

Similarly, the LCD was also developed in Japan by Dr. Koji Ebe at Takao Hospital in Kyoto, Japan [6]. He proposed the novel idea of three stages of LCD: incremental incline method for petite LCD, standard LCD, and super LCD for the medical and health care sectors that are 40%, 26%, and 12% carbohydrate, respectively. Super LCD was utilized in this case and has a macronutrient ratio of carbohydrate 12%, lipid 56%, and protein 32%, respectively [7]. In this method, total calories per day need not be restricted, and no single meal should exceed 20g, nor should any snack exceed 5g of carbohydrates. This is in contrast to the method of the Japan Diabetes Society (JDS). The JDS has proposed for years that diabetics must continue a calorie restriction diet (CRD) with the ratio of carbohydrate 50-60%, lipid 20%, and protein 20%, respectively [8].

LCD has been known to be effective for T2D so far, in which weight reduction and improved glucose variability have been observed [9]. On the other hand, Type I Diabetes (T1D) patients usually receive insulin therapy from an early stage because of an absolute shortage of insulin. However, some T1D cases show a honeymoon period associated with a certain ability of beta cells for some period [10]. Authors et al. have treated various diabetic patients and developed LCD medically and socially through the activities of the Japan LCD Promotion Association (JLCDPA) [11]. Among them, we have experienced an impressive T1D case associated with a honeymoon period and LCD continuation. Its general clinical progress and some perspectives will be described in this report.

## Case Presentation

The case is a 68-year-old female with T1D. She has no significant past medical history and no family history. She was found to have slightly elevated values of HbA1c at 6.1% and blood glucose at 118 mg/dL during her annual physical examination in September 2017. Following this, she was admitted for an emergency case in another hospital in January 2018 and was diagnosed with T1D, supported by data showing glucose levels at 459 mg/dL and HbA1c at 13.7%. Additionally, her glutamic acid decarboxylase autoantibody (GADA) levels were >2000 U/mL (normal range: <5 U/mL), and C-reactive immunoreactivity (CPR) measured 1.10 ng/mL (refer to **Table-1**).

For basic diabetic treatment, a nutritional plan was recommended, specifically a petite low carbohydrate diet (LCD). Subsequently, primary care treatment involved employing the Multiple Daily Injection (MDI) method. This included administering Lantus XR at 15 units once daily, and pre-prandial insulin glulisine three times a day, with doses of 5-3-5 units for breakfast, lunch, and dinner, respectively. Insulin glulisine is a rapid-acting modified form in which asparagine at B3 was replaced by lysine, and the lysine

**Table-1: Clinical Progress During 2017-2019**

| Date | | Examination | | | Insulin treatment | | Other laboratory data | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Year | Mon | HbA1c | GA | CPR | Rapid | Lantus | HDL | LDL | CRN | GADA |
| 2017 | 9 | 6.1 | | | | | 76 | 127 | 0.67 | |
| 2018 | 1 | 13.7 | | 1.1 | Multiple Daily Injection | | 74 | 149 | 0.54 | 2000 |
| | 2 | 9.4 | | | Multiple Daily Injection | | | | 0.61 | |
| | 3 | 7.3 | 17.0 | | Multiple Daily Injection | | 75 | 151 | 0.60 | |
| | 7 | 5.7 | | | | 15 | | | | |
| | 9 | 5.8 | 17.1 | | | 13 | | | | |
| | 12 | 5.7 | | 0.5 | | 11 | | | | |
| 2019 | 2 | 6.2 | 16.9 | | | 12 | 86 | 168 | 0.6 | |
| | 5 | 6.0 | | | | 9~11 | 79 | 136 | 0.61 | |
| | 8 | 5.8 | 17.0 | | | 10~11 | 80 | 142 | 0.57 | |
| | 10 | 6.0 | 16.3 | | | 10~11 | 90 | 168 | 0.63 | |
| | 12 | 6.1 | 16.5 | 0.3 | | 11 | 101 | 145 | 0.62 | |

*MDI: Multiple Daily Injection*

in B29 was replaced by glutamic acid. With this insulin regimen, her HbA1c and fasting blood glucose (FBG) improved for several months to 7.3% and 81 mg/dL, respectively.

## Treatment Protocol

For further evaluation and adequate treatment of T1D, she was referred to Takao Hospital. She began to restrict carbohydrate intake using the super-LCD method (refer to Figure 1). As a result, her post-prandial increase in blood glucose levels minimized. Consequently, she was able to discontinue glulisine administration three times a day. On the other hand, Lantus XR at 15 units per day was continued with instructions to adjust based on self-monitoring of blood glucose (SMBG). She reported gradually titrating Lantus XR down to 10 units by November 2018, which she continued for approximately 2.5 years with good control.

## Clinical Progress

In early 2021, SMBG values increased, while HbA1c and FBG began to hover around 6.8% and 138 mg/dL, respectively (refer to Figure 1). Lantus XR was titrated up to 13 units by June 2021. Oral ipragliflozin at 25mg once daily was added to the medication regimen in November 2021. Simultaneously, Lantus XR was temporarily decreased to 10 units daily. She currently maintains good control with ipragliflozin at 25 mg and 12-14 units of Lantus XR, both administered once daily.

CPR values consistently measured at 0.3 ng/mL until 2021, and 0.2 ng/mL after 2022. Regarding the changes observed between 2017 and 2023, laboratory findings have remained stable, with TG at 212 mg/dL (post-prandial), HDL at 76 mg/dL, and LDL at 127 mg/dL for six years. Otherwise, no remarkable changes are observed in renal function, complete blood count, and so on.

As this patient with T1D has adhered to the super-LCD for years, the daily profile of her blood glucose has remained stable up to now. For her three meals (breakfast, lunch, and supper), both pre-prandial and post-prandial glucose levels have been controlled by the super-LCD and a small dose of Lantus XR at 10-14 units per day (refer to **Fig-1**). Thus, through the continuation of the super-LCD for years, she has maintained a rather stable glucose variability, indicating a prolonged honeymoon period.

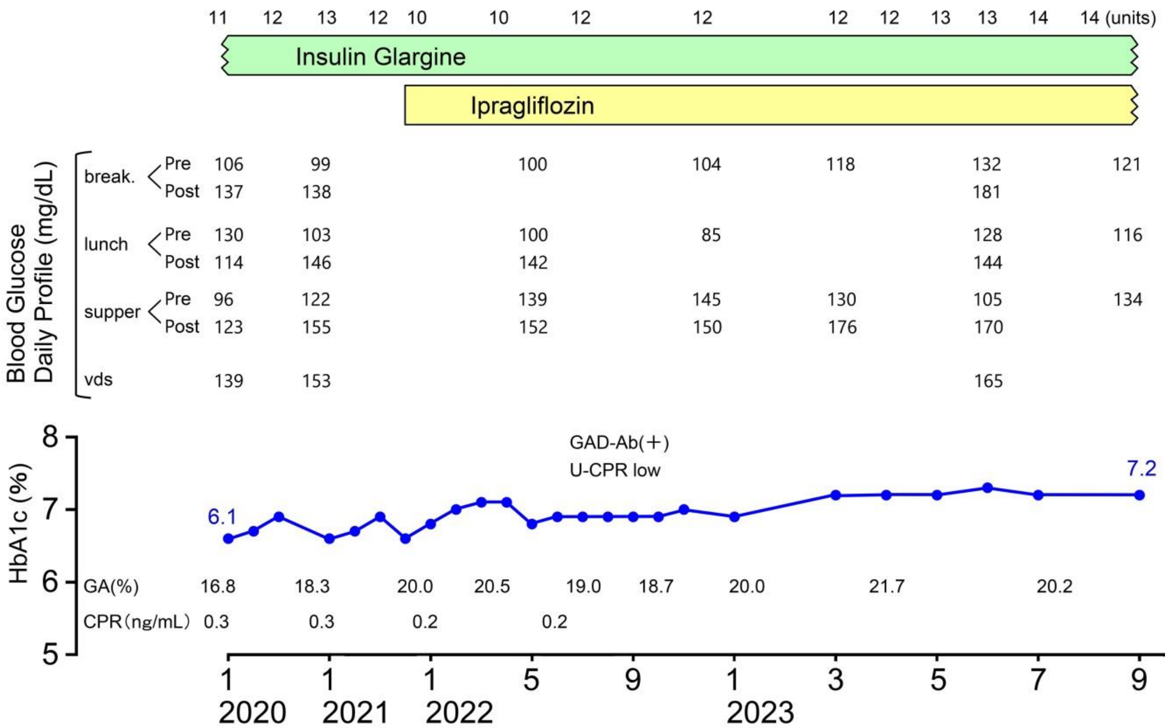


**Fig-1: Clinical progress of HbA1c and treatment after 2020**

## Ethical Standards

This case adhered to the ethical guidelines outlined in the Declaration of Helsinki. Additionally, attention was paid to the regulation of personal information, in line with standard ethical principles for both clinical practice and research. The relevant guidelines also encompassed regulations set forth by the Japanese government, including the Ministry of Education, Culture, Sports, Science and Technology, as well as the Ministry of Health, Labor, and Welfare.

The authors and co-researchers established an ethics committee specifically for this case, which operates within Takao Hospital in Kyoto, Japan. The committee comprises various professional staff members, including the hospital director, physician, head nurse, registered pharmacist, registered nutritionist, laboratory personnel, and legal professionals. The committee thoroughly deliberated on the research protocol, and informed consent was obtained from the patient through written documentation.

## Discussion

Regarding the basic medical mechanism, it is well-established that carbohydrate intake significantly influences changes in blood glucose levels, which aligns with fundamental principles of human biochemistry [12]. Atkins introduced the concept of the Low Carbohydrate Diet (LCD) in the healthcare sector for practical application [13], and clinical evidence supporting the effectiveness of LCD was reported by Shai [14]. The authors and collaborators developed three types of LCD meals: petite, standard, and super-LCD, with carbohydrate ratios calculated by calorie content as 40%, 26%, and 12%, respectively [15] Ebe. These three models were designed with convenience in mind, aligning with the three meals typically consumed daily. In this context, the LCD meal can be applied once to thrice per day, translating to petite-LCD, standard-LCD, and super-LCD, respectively. We have previously reported on the clinical efficacy of LCD for T2D patients [16], as well as for T1D patients and/or those with positive GADA [17]. Whether the diabetic patients have T2D or T1D, the continued adherence to LCD over an extended period has been clinically effective in achieving better glucose variability. Notably, both pre-prandial and post-prandial blood glucose levels show marked decreases in the daily profile, leading to a notable reduction in the mean amplitude of glycemic excursions (MAGE) [18]. The case presented in this report appears to have experienced a beneficial and prolonged honeymoon period due to the ongoing adherence to super-LCD.

Various benefits of LCD are well-documented. It allows for lower blood glucose profiles in both T1D and T2D patients, which, in turn, helps in preventing exacerbation of diabetic complications. While exogenous insulin remains essential for T1D patients, LCD has been shown to reduce the overall need for insulin. Additionally, from an economic standpoint, there are significant advantages. The financial burden associated with exogenous insulin has been a substantial barrier for many. According to ADA data, the economic costs for insulin in 2017 amounted to $15 billion dollars [19]. By minimizing insulin requirements, we not only reduce healthcare costs but also alleviate burdens on both the medical system and individual diabetic patients.

Recently, the medical costs associated with the Senior Savings Model (SSM) have been reported [20]. Out of 4.2 million Medicare cases, 1.6 million individuals benefited from this system. Among these SSM cases, approximately one-third (0.6 million) appeared to have improved insulin adherence due to lower cost-sharing. Projections for the next five years indicate an increase in insulin costs by $3.5 billion and total costs by $2.8 billion. Furthermore, it is anticipated that medical insulin will see a larger increase over 20 years, correlating with extended life-years and quality-adjusted life-years (QALY). Consequently, the rising cost of insulin has become a significant concern for lifelong treatment. Non-compliance in this regard may lead to deteriorating glycemic control. In the future, biosimilar insulin is expected to revolutionize diabetic management, holding promising clinical expectations [21].

In a similar vein to the current case, a male T1D case was reported with a prolonged honeymoon period [22]. He maintained stable glucose control without the use of oral hypoglycemic agents (OHAs) for five years. During this period, he strictly adhered to a low carbohydrate diet, along with positive specific antibodies of GAD, IA2, and ZnT8. When considering the mechanisms behind this extended honeymoon period, several perspectives can be put forth. These include i) adult onset, ii) non-specific pre-symptoms before diabetic onset, iii) a short duration of symptoms, iv) no apparent signs of ketoacidosis during the progression, v) strict adherence to a low carbohydrate diet, vi) regular strenuous exercise, and vii) unknown epigenetic and/or genetic factors.

On the other hand, high carbohydrate diets (HCDs) and insulin therapy for T1D must also be taken into consideration. Dietary sugars and starches are rapidly broken down into monosaccharides, leading to a rapid increase in blood glucose (BG) levels. Rapid-acting insulins are often used to counter BG spikes from HCDs. However, synchronizing the two large spikes of BG and insulin chronologically proves to be challenging, resulting in both hypo- and hyperglycemia. This is due to a larger variability in both estimated carbohydrate intake and the rate of insulin absorption. Dr. Bernstein refers to this phenomenon as the "Law of Small Numbers" [5].

## Limitations

This report does have some limitations. It's possible that factors influencing the onset of T1D played a role in the speed at which this particular individual progressed through the honeymoon period. While we focused on diet in this case, genetic or environmental factors may have also contributed to her prolonged honeymoon period. Additionally, successful maintenance of stable glucose variability over the years can be attributed to continued adherence to a super-LCD, as well as a consistent lifestyle, and so forth. Careful monitoring of clinical progress will be necessary in the future.

In summary, this case demonstrates a prolonged honeymoon period lasting several years after the onset of T1D, achieved through strict adherence to a low carbohydrate diet pattern. We hope this report proves to be a valuable reference for clinical research on LCD and T1D.

## Conflict of Interest

The authors have read and approved the final version of the manuscript. The authors have no conflicts of interest to declare.

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