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Glucose variability for a short period of low carbohydrate diet in diabetic patients with possible latent autoimmune diabetes in adults

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Abstract

Background: Authors have continued research for meal tolerance test (MTT) by calorie restriction diet (CRD) and low carbohydrate diet (LCD), besides M value and glucose variability.

Methods: Subjects were 38 patients of two groups. Group-1 has 19 patients (57.6±12.9 years) with type 2 diabetes mellitus (T2DM) and positive glutamic acid decarboxylase antibody (GADA), which is possible to latent autoimmune diabetes in adults (LADA). Group-2 has recruited 19 cases with T2DM and negative GADA, who showed age, sex, glucose variability-matched subjects. They were given CRD on day 1-2, and LCD day 3-14, and biomarkers were compared between Group-1 and Group-2.

Results: Average values of the daily profile of blood glucose on day2(CRD)/day4(LCD) in Group-1 vs 2 were studied. Obtained data were 202/148 mg/dL vs 205/143 mg/dL, respectively with similarity. However, M value showed 174/58 vs 179/22, respectively with difference. There were significant correlations of M value between day2 and day4 in Group-1 vs Group-2. Further, both showed contrast tendency, associated with wide distribution vs narrow distribution, respectively.

Conclusions: These results suggested that Group-1 with positive GADA may have insufficient pancreas secretion compared with that of Group-2, and these data may become a basal reference for future study of LADA.

Keywords: calorie restricted diet (CRD), glutamic acid decarboxylase (GAD), latent autoimmune diabetes in adults (LADA), low-carbohydrate diet (LCD)

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Introduction

Across the world, the number of diabetes has increased and the problem of lifestyle disease has been a crucial problem medically and socially [1,2]. Among some types of diabetes, the most prevalent one has been type 2 diabetes mellitus (T2DM), which does not usually require insulin therapy. In contrast, there is a type of acute onset diabetes, which is type 1 diabetes mellitus (T1DM) probably due to viral infection. Related to these diabetic types, there is a certain type that exists between type 1 and type 2. This type has been called latent autoimmune diabetes in adults (LADA) [3,4].

LADA has been evaluated to have characteristic points with both T2DM and T1DM clinically and immunologically [5]. As to T1DM, its genesis has been due to the autoimmune destruction of pancreas beta cells. Among them, several major anti-islet antibodies have found, including glutamic acid decarboxylase autoantibody (GADA). Further, GADA is also found in some patients with T1DM [4].

In the clinical practice for diabetes, patient with T2DM and positive GADA has been occasionally found. In such a case, the patient is not necessary for insulin therapy during the early period. This type of diabetes has been called as slowly progressive insulin-dependent (type 1) diabetes mellitus (SPIDDM) in Asian countries and Japan [6]. In contrast, it is called LADA in the North American Region and European countries [3,7].

In light of the definition of LADA, Immunology of Diabetes Society (IDS) presented the guideline. Among them, there are three main items, which are 1. adult age of onset usually more than 30 years, 2. insulin independence at onset for at least six months, 3. positive results for islet-cell autoantibodies [8]. On the other hand, various controversy and discussion have been found. It seems to be not easy to obtain the clarified diagnostic guideline so far. For LADA, there are heterogeneous situations from immunologic, genetic, and phenotypic features. Consequently, the cause of these phenomena is likely to be due to autoimmune variability, insulin resistance, or pancreatic beta cell damage [9].

For the therapy of diabetes, the standard nutritional treatment was formerly a calorie restriction diet (CRD). After that, another type of diet therapy has been begun. It was a low carbohydrate diet (LCD) proposed by Bernstein and Atkins in 1980-1990' in North American countries [10,11]. Consecutively, LCD has been accepted and known, and lots of papers about the efficacy of LCD were found.

From the evidence-based medicine (EBM) point of view, there was a Dietary Intervention Randomized Controlled Trial (DIRECT) study [12]. Moreover, follow up study of DIRECT was reported [13], and recently consecutive investigations for the effects of LCD have been continued [14,15]. Various reports with a clinical predominance of LCD have been found so far.

On the other hand, authors have started LCD in Japan [16]. We have continued to develop LCD in various situations such as medical practice, workshop, textbook, and other opportunities, through the activity of Japan LCD Promotion Association (JLCDPA). We proposed three kinds of LCD, which are super-LCD, standard-LCD, and petite-LCD [17]. Clinical research has also been continued including ketone bodies in the case of LCD and the physiological axis of a pregnant mother, newborn, and placenta [18]. Furthermore, we have continued research about CR and LCD for meal tolerance test (MTT), insulinogenic index (IGI), and so on [19,20].

Furthermore, we have studied the daily profile of blood glucose in patients with T2DM for the comparison between CRD and LCD. Among lots of T2DM, some cases with positive GADA are found, which would be possibly changing to LADA for several years. In this study, we investigated the detail aspect of the cases of T2DM with positive GADA.

Methods

The enrolled subjects in the current study were 38 patients with T2DM, who have been recently diagnosed to be T2DM. These patients were admitted to the hospital for two weeks. The purpose is to give further evaluation and treatment of diabetes, which has been called the educational admission for diabetes. For two weeks, they have taught 1) fundamental knowledge for diabetes, 2) experience of conventional diet therapy which is CRD, 3) experience and continuation of LCD, 4) other examination and treatment.

In this study, there are two groups of T2DM. Group-1 includes 19 patients showing the positive result for GADA. The presence of GADA has the possibility of a relationship with LADA in the future, though they are T2DM at present. Thus 19 patients were categorized into Group-1 (Table 1). Subjects in Group-1 had the examination of lipids including triglyceride, HDL-C, and LDL-C on day 2 and day 14, which was shown in Table 2.

In contrast, Group-2 included 19 patients with T2DM. Authors and colleagues have a long history of clinical research for many diabetic patients who had received the same protocol for 14 days. From such data, 19 patients were picked up who showed similar results of age, sex, HbA1c, glucose variability to those of 19 patients in Group-1. Thus, we selected 19 patients for Group-2. The general background and data of Group-1 and 2 are shown in Table 3.

Authors and colleagues have continued diabetic clinical research and have applied our common diabetic formula protocol for examination. It has the detail items for the diagnosis, examination, and therapy for a diabetic research program. Its general principle is shown in the following:

1. Diagnosis: the subjects in the current study was T2DM in the recent period. Patients with specific types of diabetes were excluded such as type 1 diabetes mellitus (T1DM), gestational diabetes, and others. These patients were admitted without anti-diabetic agents for diabetes, because those medicines may influence blood glucose variability during daily profile, preprandial, and postprandial glucose responses.

2. Exam protocol: Our protocol has 14 days of detail evaluation and treatment for T2DM. On the next day of their admission (day 2), blood samples are drawn for basal biomarker tests after overnight fasting. General blood tests have complete blood count, renal and liver function tests, lipids, and others. As to diabetes, several specific items were measured on fasting and postprandial time, besides immunoreactivity of insulin (IRI), HbA1c, C-peptide immunoreactivity (CPR), HOMA-R, HOMA-β, and etc.

3. CRD: Our protocol includes CRD on day 1 and day 2. CRD includes 1400 kcal per day and its PFC ratio is been 15: 25: 60. This ratio has been for long the standard Japanese meal pattern from the Japan Diabetes Association (JDA) [21].

4. LCD: After CRD, subjects were provided LCD meal from day 3 to day 14. LCD has 1400 kcal per day and it has 12% of carbohydrate in calorie ratio. This type of LCD has been called as super-LCD, which has been known in Japan. Our protocol has three kinds of LCD, which are super LCD, standard LCD, petite LCD with a carbohydrate ratio of 12%, 26%, 40%, respectively.

5. Comparison of diet: In our protocol, some biomarkers are compared between day 2 and day 4. Daily profile of blood glucose was compared between day 2 and day 4. Furthermore, the comparison of serum lipids such as triglyceride, HDL-cholesterol, and LDL-cholesterol was performed between day 2 and day 14.

6. Blood glucose profile: In order to study the daily profile of blood glucose in the enrolled subjects, glucose values were checked seven times per day. The clock time was 08h, 10h, 12h, 14h, 17h, 19h, 22h, respectively. The standard meal of CRD was given to the patients on day 1 and day 2. Then, the daily profile of blood glucose was measured in day 2. Consecutively, the standard meal of LCD was given from day 3 to day 14. Then, blood profile was measured in day 4. In summary, the glucose profile was studied and compared between day 2 and day 4. Former is on CRD and the latter is on LCD. After obtaining the blood glucose values, these data were converted to M value by using the equation formula of M value. It expresses numerical value, that means average blood glucose and mean amplitude of glycemic excursions (MAGE) [22,23].

M value

In order to study the glucose variability for a diabetic case in the daily profile, M value can become a preference biomarker. Glucose variability has two aspects, which are 1) average blood glucose per day, and w) the degree of swinging level of glucose that is MAGE [22,23]. M value shows a numerical value including and meaning of both data. By estimating the level of M value, we can evaluate the stability of glucose variability.

M value can be obtained by the calculation using the equation of the logarithmic transformation. From the clinical significance point of view, M value would be suggestive of the deviation degree from the ideal profile of the daily profile of the blood glucose per day [24,25].

The actual method for calculation for M value from the data of glucose are described as follows: 1. At first, the basal equation is $M = M^{BS} + M^{W}$. The meaning of the M value is the sum total of the values of M^{BS} and M^{W}. 2. Second, M^{W} can be calculated by (maximum blood glucose – minimum glucose)/20. 3. Third, M^{BS} shows the mean value of the MBSBS. As the three steps would be combined together in one equation, MBSBS means the individual M value, that can be revealed as (absolute value of $[10 \times \log (\text{blood glucose level}/120)])^3$.

Because M value has been estimated to be the deviation degree of the glucose variability from the ideal situation of blood variability, the standard normal range of M value has been known. When obtaining the result of the M value, the usual evaluation is in the following: normal range is less than 180, borderline is 180 and more than 180 and less than 320, the abnormal range would be 320 and more than 320 [24,25].

Statistical analysis

The results of the data in this study were revealed by the statistic way of mean and standard deviation. For some biomarkers, the obtained data were shown as the median value and the quartiles of 25%/75%. Further, the boxplot figure method was adopted in this research. It includes the value of the median, quartiles of 25%/75% values, maximum and minimum data.

In the case of analyzing the correlations among some biomarkers, we used the Spearman test and calculated the correlation coefficients. Further, we applied the computerized medical statistical tool for standard analyses for several biomarkers [26].

Ethical considerations

The current study was fundamentally conducted in compliance with the adequate ethical principles based on the previous Declaration of Helsinki. In addition, there was some commentary for the Ethical Guidelines for Research in the medical field for human beings and in the

conduction of the Good Clinical Practice (GCP). As regards the protection of human rights, there were some ongoing considerations. Moreover, “Ethical Guidelines for Epidemiology Research” was applied in accordance with the related guideline. Those principles were from Japan by the Ministry of Education, Culture, Sports, Science and Technology and also by the Ministry of Health, Labor and Welfare. Authors and co-researchers have prepared the related ethical committee. Regarding various ethical and medical problems, enrolled specialists were physician, nurse, nutritionist dietitian, pharmacist, and other experts in the legal specialty on the management of the hospital.

Concerning the current study, the discussion conducted by specialists were appropriate and valid, associated with the agreements. As regards to this study, informed consents and written document agreements were obtained from all the subjects. This investigation has been registered by the National University Hospital Council of Japan, which is #R000031211.

Results

Fundamental data

The results from 19 patients with T2DM with positive GADA were shown in Table 1. The average age was 57.6 ± 12.9 years old (mean ± SD) and the number of male/female was 10/9, respectively. Average HbA1c was 7.2%. As basal data, the median values of GADA, HOMA-R, and HOMA-β were 81.9 U/mL, 3.3, and 29.3, respectively.

Table 1. Biomarkers in the subjects with positive GAD-antibody

		Mean ± SD	Median (25% - 75%)
Subjects			
	Number	19	19
	Sex (male/female)	10 / 9	10 / 9
	Age (years)	57.6 ± 12.9	59 (49 - 68)
Basal			
	HbA1c (%)	7.2 ± 1.4	7.2 (6.5 - 7.8)
	GADA (U/mL)	113 ± 121	81.9 (58.4 - 112)
	HOMA-R	3.6 ± 2.1	3.3 (2.8 - 4.3)
	HOMA-β	38.5 ± 40.4	29.3 (14.6 - 42.3)
MTT			
	Glucose - 0 min (mg/dL)	156.9 ± 45.7	163 (115 - 178)
	Glucose - 30 min (mg/dL)	197.6 ± 61.4	212 (143 - 228)
	IRI - 0 min (U/mL)	8.1 ± 4.8	7.2 (4.9 - 10.5)
	IRI - 30 min (U/mL)	14.8 ± 6.3	14.9 (8.6 - 18.0)
LCD intervention			
	Average glucose (day 2) (mg/dL)	202.4 ± 60.1	188 (169 - 255)
	Average glucose (day 4) (mg/dL)	148.1 ± 41.2	148 (119 - 169)
	M value (day 2)	174.6 ± 182.1	77.7 (54.2 - 284)
	M value (day 4)	58.9 ± 69.6	27.3 (9.5 - 76.4)

HbA1c: Glycolyzed hemoglobin level, GADA: Glutamic acid decarboxylase antibody, HOMA-R: Homeostatic model assessment for insulin resistance, HOMA-β: Homeostatic model assessment for β-cell function, MTT: Meal tolerance test (carbohydrate 70g), IRI: Immuno-reactive insulin, LCD: low-carbohydrate diet

Meal tolerance test

As meal tolerance test (MTT), breakfast of CRD with 70g of carbohydrate was provided to the subjects in the morning on day 2 after an overnight fast. The results of glucose and IRI on 0 min and 30 min are 157 to 198 mg/dL, 8.1 to 14.8 U/mL, respectively (Table 1).

Daily profile of glucose

The average value of daily profile of blood glucose on day 2 vs day 4 was 202.4 mg/dL vs 148.1 mg/dL, respectively. When the data were analyzed into M value, the median level on day 2 vs day 4 was 77.7 vs 27.3, respectively (Table 1).

Table 2. Lipid profiles in the subjects with positive GAD-antibody

		Mean ± SD	Median (25% - 75%)
Lipids			
	Triglyceride on day 2 (mg/dL)	128.6 ± 81.7	109 (87 - 134)
	Triglyceride on day 14 (mg/dL)	83.8 ± 46.9	75 (59 - 94)
	HDL-Chol on day 2 (mg/dL)	72.9 ± 25.3	63 (57 - 87)
	HDL-Chol on day 14 (mg/dL)	63.7 ± 25.8	56 (45 - 75)
	LDL-Chol on day 2 (mg/dL)	133.5 ± 40.4	135 (110 - 146)
	LDL-Chol on day 14 (mg/dL)	136.3 ± 55.5	133 (110 - 157)
	RLP-Chol on day 2 (mg/dL)	6.3 ± 4.3	4.7 (3.4 - 7.8)

HDL: High-density lipoprotein, LDL: Low-density lipoprotein, RLP: Remnant-like particle, Chol: Cholesterol

Lipid profile

Lipid profiles were studied on day 2 and 14 after overnight fasting. The results of triglyceride, HDL-C, LDL-C on day 2 vs day 14 were 109 vs 75 mg/dL, 63 vs 56 mg/dL, 135 vs 133 mg/dL, respectively (Table 2). The value of triglyceride showed a significant decrease between day 2 and day 4 ($p<0.05$). In contrast, the levels of HDL-C, LDL-C, or RLP-C did not show significant changes.

Table 3. Equality of two groups with positive and negative GAD-antibody

Group		Group-1	Group-2
		GADA (+)	GADA (-)
Subjects			
	Number	19	19
	Sex (male/female)	10 / 9	10 / 9
	Age (years old) (Mean±SD)	57.6 ± 12.9	57.4 ± 13.7
	Median (25% - 75%)	59 (49 - 68)	58 (48 - 70)
	Average glucose (day 2) (mg/dL)	202.4 ± 60.1	205.7 ± 61.8
	Median (25% - 75%)	188 (168 - 255)	182 (164 - 256)
	Average glucose (day 4) (mg/dL)	148.1 ± 41.2	143.4 ± 31.3
	Median (25% - 75%)	148 (118 - 169)	135 (121 - 160)
	M value (day 2) (Mean±SD)	174.6 ± 182.1	179.7 ± 187.9
	Median (25% - 75%)	77.7 (54.2 - 284)	81.8 (50.4 - 300)
	M value (day 4) (Mean±SD)	58.9 ± 69.6	22.8 ± 42.1
	Median (25% - 75%)	27.3 (9.4 - 76.3)	6.9 (4.2 - 24.8)

GADA: Glutamic acid decarboxylase antibody

Changes in average blood glucose

According to the various data of 19 subjects in Group-1, suitable 19 subjects with T2DM were enrolled for Group-2 from the points of age, sex, and average glucose. The comparative data from Group-1 and Group-2 were shown in Table 3. Among them, similar results were found in age, average glucose.

As to glucose decrease from day 2 to day 4, both groups showed similar degree. Data were 202.4 to 148.1 mg/dl in Group-1, and 205.7 to 143.4 mg/dL in Group-2. However, in the case of M value, there was a different result. M value showed the decrease from 174.6 to 58.9 in Group-1, and it showed from 179.7 to 22.8 in Group-2 (Table 3). Consequently, there was a discrepancy in Group-1 and Group-2, which are the LADA group and usual T2DM group, respectively.

There are significant correlations between average blood glucose and HbA1c ($p<0.05$), and between average blood glucose and M value ($p<0.01$) (Figure 1a-b).

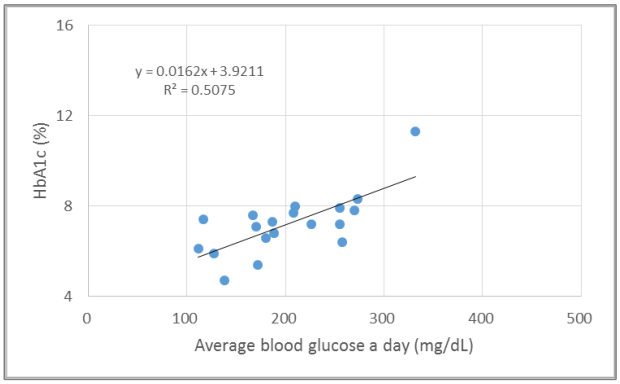

Figure 1a. Correlation between average blood glucose and HbA1c. There was a significant correlation between them ($p<0.05$).

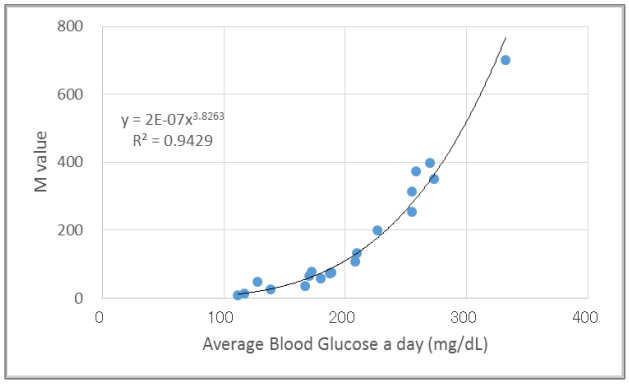

Figure 1b. Correlation between average blood glucose and M value. There was a significant correlation between them ($p<0.01$).

Comparison of glucose variability

There were significant correlations of average blood glucose between day 2 and day 4 in Group-1 (Figure 2a) ($p<0.01$), and also in Group-2 (Figure 2b) ($p<0.01$). Both regression curves show similar slope data, while both distributions show a little difference. In other words, Group-1 reveals a somewhat wider distribution than that of Group-2.

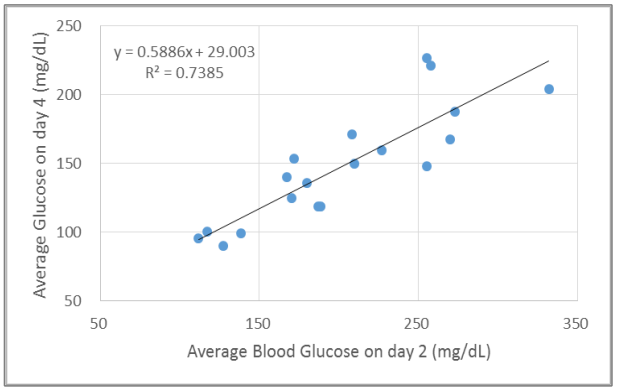

Figure 2a. Correlation between day 2 and 4 in Group-1. There was a significant correlation between them ($p<0.01$). The slope of the line is 0.59.

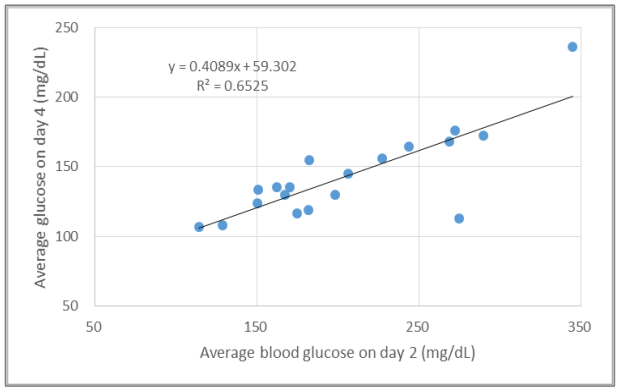

Figure 2b. Correlation between day 2 and 4 in Group-2. There was a significant correlation between them ($p<0.01$). The slope of the line is 0.40.

Correlation of M value

There were significant correlations of M value between day 2 and day 4 in Group-1 ($p<0.05$). It showed a rather wide distribution (Figure 3a). One of the reasons is from the 4 cases with higher M value out of 19 cases. On the other hand, there was a significant correlation of M value between day 2 and day 4 in also Group-2 ($p<0.01$). It showed very narrow distribution, associated with extremely high correlation coefficient (R2 = 0.95) (Figure 3b).

Decrease of M value

In Group-1 and Group-2, the data of M value were calculated into the boxplot method (Figure 4). The level of the box means the quartiles of 25% and 75%. There were similar situations on day 2 in Group-1 and Group-2. On day 4, there was a remarkable decrease in the level of the box (distribution from 25% to 75%) in Group-2 (T2DM). In contrast, in Group-1 (positive for GADA), the level of the box did not decrease so much compared with that of in Group-2.

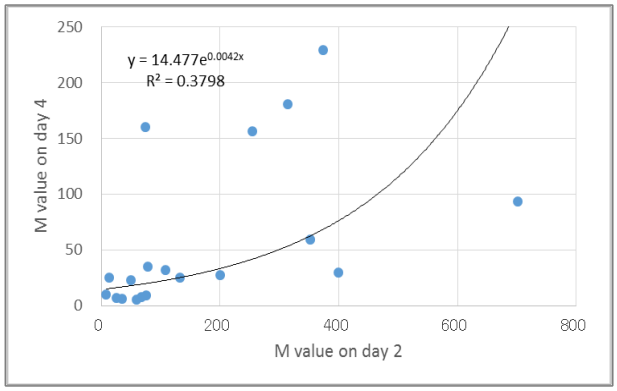

Figure 3a. Correlation between day 2 and 4 in Group-1.
There was a significant correlation between them ($p<0.05$).

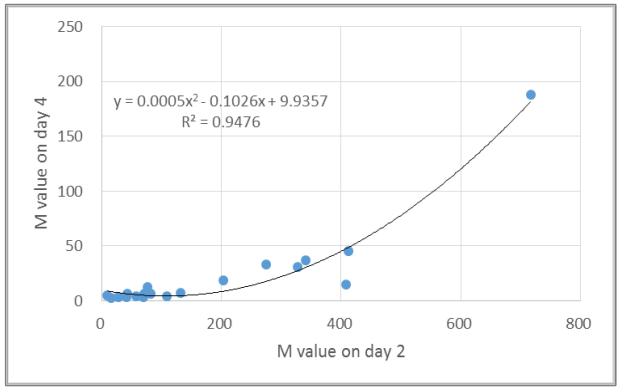

Figure 3b. Correlation between day 2 and 4 in Group-2.
There was a significant correlation between them ($p<0.01$).

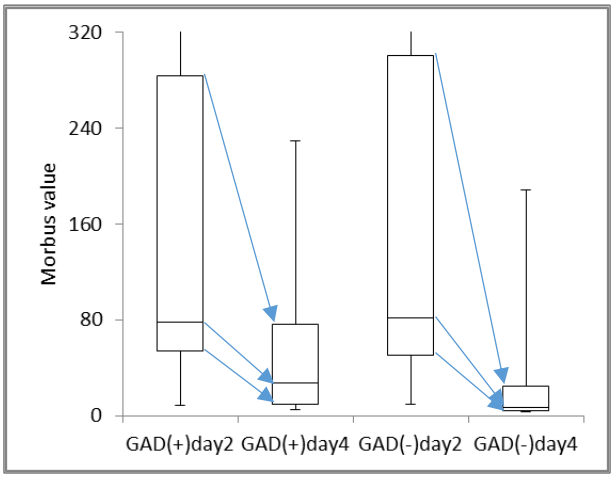

Figure 4. Comparison of M value for day 2 and 4 in Group-1 and 2.
Group-1 (left): positive for GAD with a moderate decrease of M value.
Group-2 (right): negative for GAD with a remarkable decrease of M value.

Discussion

Subjects enrolled in the current study were 19 patients with T2DM and positive results of GADA. As for the age of the subjects, median 50% of the distribution was 49-68 years old, which appears to be equal to or slightly younger than subjects who have been treated at our regular diabetes outpatients [27]. Both the mean and median HbA1c levels were 7.2%, which would be a mild degree. The median values of HOMA-R and HOMA-β were 3.3 and 29.3, which were about moderate data. The antibody titer of GADA was 81.9 (58.4-112) (normal range is less than 5.0), and there were no cases showing a remarkably higher GADA in these subjects [4,5].

From the data of glucose and IRI on 0 and 30 min for meal loading, the research of MTT has been developed. In order to evaluate the insulin secretion, carbohydrate loading has been performed [28]. There are several methods including intravenous glucose tolerance test (IVGTT) and 75g oral glucose tolerance test (75gOGTT) [29]. Recently, MTT has been conducted into clinical practice and research.

Authors have continued clinical research on CRD and LCD for long. Among these, we have evaluated pancreas function by MTT using 70g of carbohydrate in the breakfast of standard CRD. Accumulating these data, we have proposed the insulinogenic index (IGI)-carbo70 [30]. For reference, there are some kinds of formula breakfast. They include carbohydrate-breakfast (PFC = 15:20:65%), protein-breakfast (PFC = 35:20:45%), and others [31]. According to each research project, a certain formula can be used. Furthermore, the authors

proposed the analyzing way of the area under the curves (AUC) of glucose and insulin [32]. These studies would become fundamental data for future research in this field.

In this study, administration of the LCD for only two days reduced the mean blood glucose level by 54.3 mg/dL, and the M value also remarkably decreased. These results suggest the short-term effects of super-LCD on diabetes [12]. The reason for the efficacy would be the included ratio of carbohydrate, which is 12% with the minimum of an ordinary meal.

As for lipids, TG decreased from 109 mg/dL to 75 mg/dL in median for 12 days. It has been known that the triglycerides level would be decreased by LCD in the short term [33]. Our result was consistent with the previous reports [14].

The study protocol included the recruited 19 cases of T2DM (Group-2) correspond to 19 cases with positive GADA (Group-1). Because of almost the same data of age, sex, average glucose, and M value on day 2, the recruited result seemed to be successful. There was a difference of decreased M value in Group-1 and 2, suggesting the less glucose-lowering effect in Group-1.

It has been known that patients with LADA may show slower decreasing pancreas function for years. Moreover, it is possible that they may have a lower reserve ability to secrete insulin in a shorter period [34]. This possible pathophysiology could be raised by our current research protocol.

There was a significant logarithmic correlation between average blood glucose and M value with a remarkable high coefficient. It suggested that average glucose value may play a crucial role in the level of M value [35,36].

Regarding the correlation of average blood glucose between day 2 and day 4, the regression curve was y=0.59x + 29.0 and y=0.41x + and 59.3. When we put 150 into x (day 2), then y (day 4) becomes 117.5 vs 110.8, in Group-1 vs 2, respectively. When we put 300 into x, then y becomes 206 vs 182 in Group-1 vs 2, respectively. Thus, the value of day 4 would be calculated to be higher in Group-1 compared with Group-2. These results suggest that cases in Group-1 may have less ability of insulin secretion than that in Group-2 [34].

When we consider the results of Figure 2 and Figure 3 together, we would speculate the interrelationship among average blood glucose, M value, fluctuation of blood glucose and MAGE [24,25]. In addition to the boxplot study with median and quartile distribution of 25%/75% (Figure 4), subclinical impaired secretion of insulin in some cases could be elucidated by a series of analysis methods [37].

In this study, we investigated the detail of patients with LADA. The characteristic point of LADA would be a conceptual phenotype that exists between conventional T1DM and T2DM. Recently, there has been some clinical issues and challenges for LADA [38]. They include the prevention of progressive beta cell failure by DPP4 inhibitors, GLP-1 analogs, metformin, and insulin [39]. Furthermore, there was an investigation of islet cells and exocrine pancreatic tissues in the pancreas for LADA which were positive for GADAs and ICAs [40].

According to the study on GADA in 32 patients with LADA, 59% of them showed positive results for the measurement of GADA-ELISA method [41]. Patients with positive ELISA had significantly lower insulin secretion, suggesting the presence of more cytotoxic GAD epitopes. Consequently, measuring the value of GADA may predict the ability of insulin secretion in patients with LADA.

In the Action LADA Study, the majority of subjects showed positive for GADA, while only 24.1% of subjects were positive for at least two autoantibody types [42]. There is some controversy concerning the pathogenesis of LADA, which has not been clarified yet. A recent study revealed a significant association between IA-2 positivity and increased body mass index (BMI) [43]. It may suggest two possibilities in obese or lean subjects for LADA. One is persisting low-grade inflammation with genetic susceptibility to T2DM in obese people, and another is specific immunological involvement with genetic susceptibility to T1DM in lean people [43].

From various studies, the incidence rate of the adult-onset autoimmune diabetes has been different in countries and ethnicity. It is rather higher in North Europe than American, Latino, and Asia [44,45]. The prevalence of LADA has been reported as follows: 2.6% in United Arab Emirates, 3.2% in India, 4.4%-5.3% in Korea, 5.7% in China, 7.0-14.0% in North Europe [45,46]. In these studies, however, there have been various differences in study design, method and criteria, where we have to compare the data of incidence and prevalence from a different area in the world.

Our current research has its limitation. The protocol included that the patients were clinically diagnosed as T2DM as well as the presence of positive GADA, without the possibility of acute onset of type 1A. In this situation, there is the possibility that some patients were T2DM, and other patients possibly would develop SPIDDM. Although its frequency cannot be unknown at this point, the diagnosis will become clear after following up the clinical course several years. There are some reports of the relationship with HLA-DR9 in the case of Japanese patients with SPIDDM. In our current research, however, HLA has not been scrutinized. Consequently, further evaluation would be necessary for the future, with careful observation of the states of these patients.

In summary, nutritional therapy was changed from CR to LCD in 19 patients with GADA positive T2DM (Group-1), and changes in mean blood glucose and M levels were examined. In addition, 19 cases with age-, sex-, data-matched laboratory values were selected (Group-2). Comparing both groups, Group-1 had slightly less reduction in blood glucose. For GADA-positive cases, it is necessary to follow up their insulin secretory capacity on a long-term basis. Current data will serve as a basis for future clinical studies of SPIDDM.

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Conflict of interest

The authors state that they have no conflicts of interest in this study.

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