

## CR and LCD dietary therapy for diabetic patients: Usefulness of M value

### Running title: M value for glucose variability in CR and LCD

Hiroshi Bando <sup>1\*</sup>, Koji Ebe <sup>2</sup>, Tetsuo Muneta <sup>3</sup>, Masahiro Bando <sup>4</sup> and Yoshikazu Yonei <sup>5</sup>

<sup>1</sup> Tokushima University/Medical Research, Tokushima, Japan. Email: pianomed@bronze.ocn.ne.jp

<sup>2</sup> Takao Hospital, Kyoto, Japan. Email: koji.ebe@gmail.com

<sup>3</sup> Muneta Maternity Clinic, Chiba, Japan. Email: czf06641@nifty.com

<sup>4</sup> Department of Nutrition and Metabolism, Institute of Biomedical Sciences, Tokushima University Graduate School, Tokushima, Japan. Email: b\_moppy@hotmail.com

<sup>5</sup> Anti-Aging Medical Research Center, Graduate School of Life and Medical Sciences, Doshisha University, Kyoto, Japan. Email: yyonei@mail.doshisha.ac.jp

\***Corresponding author:** Hiroshi Bando, Tokushima University/Medical Research, Tokushima, Japan; Email: pianomed@bronze.ocn.ne.jp

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#### Abstract

**Background:** There have been continuing discussion about Calorie Restriction (CR), low carbohydrate diet (LCD) and efficacy of LCD. We have treated lots of diabetic patients and reported clinical significance of LCD and ketone bodies. In current study, Morbus (M) value for blood glucose variability were investigated in CR and LCD, with proposal for usefulness of clinical and research field.

**Subjects and Methods:** Subjects included 52 patients with Type 2 Diabetes Mellitus (T2DM), which were male 21, female 31, 58.9±12.1 y.o.in average, 60 y.o.in median. They were admitted and provided CR diet (60 % carbohydrates, 1400 kcal/day) on day 1-2, and LCD (12 % carbohydrate, 1400 kcal/day) on day 3-14. Methods were as follows:1) basal biomarkers and daily profile of blood glucose (7 times) on CR were measured on day 2, 2) similarly, glucose profile on LCD were measured on day 4, 3) Triglyceride, uric acid and other markers were measured on day 12. 4) Morbus (M) value in glucose variability was investigated.

**Results:** By the level of M value, subjects were classified into 4 groups. M value ranged from 13.6 to 425.6 on day 2 (CR) and from 9.0 to 82.1 on day 4 (LCD). The average HbA1c in 4 groups were 6.2 %, 7.0 %, 8.1 %, 9.0 %, respectively. Blood glucose on day 4 was significantly decreased compared with those on day 2 in each group. M value was significantly decreased from day2 to day 4 in group 2, 3, 4. Triglyceride on day 14 was significantly decreased compared with those on day 2 in each group. There was significant correlation between HbA1c and M value on day 2, between average blood glucose and M value on day 2, 4, and between M value of CR and LCD on day 2, 4.

**Discussion and Conclusion:** The efficacy of LCD was observed from day 2 to day 4, with significant decrease in glucose and M value. The carbohydrate amount was decreased from 210g (CR) to 42g (LCD) per day, resulting decrease of average blood glucose and M value. These findings suggest that M-value would be useful marker for treatment of T2DM clinically and research development in glucose variability.

**Keywords:** low carbohydrate diet (LCD), Morbus value (M value), type 2 diabetes mellitus (T2DM), Calorie Restriction (CR), glucose variability.

## Abbreviations

LCD: Low-Carbohydrate Diet; CR: Calorie Restriction;

T2DM: Type 2 Diabetes Mellitus;

MAGE: Mean Amplitude of Glycemic Excursions; M-value: Morbus value;

HOMA-R: Homeostasis Model Assessment insulin Resistance;

HOMA- $\beta$ : Homeostasis Model Assessment Beta-cell function.

## Introduction

There have been continuing discussion concerning Calorie Restriction (CR) and low carbohydrate diet (LCD). As to the efficacy of LCD, several significant reports were observed [1-6]. Thus, clinical significance of LCD has been prevalent in recent years.

We have treated lots of patients with diabetes mellitus, and investigated the efficacy of LC [7-9]. Furthermore, we reported the clinical significance of ketone bodies in LCD and in physiological role of pregnant female and fetus-newborn axis [10, 11].

Blood glucose variability in diabetic patients have been important to be investigated using several methods. Schlichtkrull, Service and others reported the usefulness of M-value which is one of the index of blood sugar level and mean amplitude of glycemic excursions (MAGE) [12-15]. This index would be applicable for evaluation of the control of diabetic patients, but M-value has not been so widely used for diabetic research.

Including these circumstances mentioned above, we investigated the M-value on CR and LCD in diabetic patients in this study, and clarified the clinical usefulness of this marker, expecting further development of research for blood glucose variability in CD and LCD.

## Subjects and Methods

The subjects included 52 patients with diabetes mellitus, which were 21 males and 31 females, with age groups ranging between 32-78 years old,  $58.9 \pm 12.1$  (mean  $\pm$  SD) years old in average, 60 years old in the median value. They were admitted for 14 days, and received the same treatment protocol for endocrine and metabolic examination.

The study began with providing a controlled diet for the patients. Calorie Restriction (CR) diet was given on day 1 and 2, which contained 60 % carbohydrates, 25 % lipids and 15 % protein with 1400 kcal/day. Successively, Low Carbohydrate Diet (LCD) was given from day 3 until day 14, which contained 12% carbohydrates, 64 % lipids and 24 % protein with 1400 kcal/day, namely super LCD formula used for long years in our nutritional investigation for LCD [7- 9,11].

The examination protocol was as follows: On day 2, we measured the basal biomarkers and daily profile of blood glucose at the second day of providing CR diet. On day 4, we measured daily profile of blood glucose at the second day of providing LCD. On day 14, serum triglyceride and uric acid and other biomarkers were measured.

### Analysis Method

The results for the daily profiles of blood glucose on day 2 and 4 were analyzed with the following method. Firstly, Data from 52 cases were calculated for mean, standard deviation, median, Morbus (M) value, and so on.

Secondly, 52 cases were categorized for 4 groups according to the obtained value of M value, and analyzed, in which each group includes 13 cases.

### Analysis for M-value

In order to investigate blood glucose variability, Schlichtkrull and others proposed new marker, namely Morbus (M) value. The M-value is a logarithmic transformation of the deviation of glycemia from an arbitrary assigned “ideal” glucose value, with an expression of both the mean glucose value and the effect of glucose swing [12-16].

M value is calculated by the following the formula:  $M = M^{BS} + M^W$ , where  $M^W = (\text{maximum blood glucose} - \text{minimum glucose})/20$ ;  $M^{BS} = \text{the mean of MBSBS}$ ;  $MBSBS = \text{individual M-value for each blood glucose value calculated as } (\text{absolute value of } [10 \times \log(\text{blood glucose value}/120)]^3)$ . The formula is shown in Figure 1. [12, 13]

$$M\text{-value} = \frac{\sum}{N} \left| M \frac{BS}{BS} \right| + W/20 \quad \text{where} \quad M \frac{BS}{BS} = \left| 10 \log \frac{PG}{120} \right|^3$$

Figure 1: The calculation of Morbus (M) value

As to the interpretation for the M value, the standard range is <180, borderline is 180-320 and abnormal is >320. There were discussion concerning how many times of sampling per day is necessary. It was reported that multiple sampling and a 7-point glycemic trial per day would have yielded similar results [15, 17].

### Statistical analyses

In this study, data was represented as the mean +/-standard deviation. For statistical analyses, correlation coefficients (Pearson) were calculated using the JMP (Version 8) statistical analysis software (JMP Japan Division of SAS Institute Japan Ltd., Minato-ku, Tokyo, Japan) and Microsoft Excel analytical tool. Intergroup comparisons were made using the

Wilcoxon rank sum test or the Bonferroni multiple comparison (Lambert method). A significance level of less than 5 % obtained using a two-tailed test was considered to be statistically significant.

## Ethical Considerations

Current study was conducted in compliance with the ethical principles of the Declaration of Helsinki and Japan's Act on the Protection of Personal Information along with the Ministerial Ordinance on Good Clinical Practice (GCP) for Drug (Ordinance of Ministry of Health and Welfare No. 28 of March 27, 1997). No ethical committee meeting was held. Informed consent was obtained from the subjects concerning this questionnaire. The study was registered with UMIN #R000031211.

## Results

### 1) Fundamental data

The data obtained from 52 subjects was shown in Table 1. By the level of M value, subjects were classified into 4 groups. The Average M value ranged from 13.6 to 425.6 on day 2, (CR) and from 9.0 to 82.1 on day 4 (LCD). The average HbA1c value in 4 groups were 6.2 %, 7.0 %, 8.1 %, 9.0 %, respectively. Blood glucose level on day 4 was significantly decreased compared with those on day 2 in each group. Triglyceride level on day 14 was significantly decreased compared with those on day 2 in each group.

Table 1. Basal Biomarkers in 4 groups classified by the M value

		group 1	group 2	group 3	group 4	
Subjects	number (M/F)	13 (7/6)	13 (3/10)	13 (5/8)	13 (6/7)	
	age(y.o.)					
	M±SD	51.8 ± 12.0	60.5 ± 17.6	64.5 ± 8.2	59.9 ± 6.0	
	median	57.0	68.5	64.0	61.5	
M value	(day 2)	M±SD	13.6 ± 7.9	50.3 ± 15.3	141.2 ± 33.2	425.6 ± 179.4
		median	12.8	47.3	139.5	396.6
	(day 4)	M±SD	9.0 ± 7.9 ns	10.8 ± 11.6 **	19.2 ± 11.8 **	82.1 ± 54.1 **
		median	5.8	7.3	17.6	85.3
HbA1c (%)	M±SD	6.2 ± 0.8	7.0 ± 1.0	8.1 ± 0.8	9.0 ± 1.1	
	median	6.2	7.0	8.0	9.1	
Blood Glucose (mg/dL)	(day 2)	M±SD	132.6 ± 11.0	162.1 ± 16.0	203.8 ± 19.5	284.7 ± 33.5
		median	132.7	166.8	208.3	283.0
	(day 4)	M±SD	110.8 ± 17.2 *	127.9 ± 23.1 **	155.2 ± 12.7 **	188.9 ± 35.0 **
		median	104.6	129.8	154.2	200.6
Insulin level (μL/mL)	M±SD	7.7 ± 4.4	7.2 ± 4.5	6.0 ± 4.0	6.5 ± 4.6	
	median	6.4	7.5	4.1	5.6	
HOMA-R	M±SD	2.4 ± 1.5	2.4 ± 1.6	2.7 ± 2.1	3.5 ± 2.3	
	median	2.3	2.1	1.7	3.0	
HOMA-β	M±SD	48.8 ± 29.3	39.5 ± 23.2	22.2 ± 16.2	15.3 ± 12.7	
	median	38.5	29.3	16.8	11.7	
Triglyceride (mg/dL)	(day 2)	M±SD	118.3 ± 54.7	102.1 ± 67.8	103.0 ± 38.6	180.3 ± 58.1
		median	133.0	97.0	96.0	187.0
	(day 12)	M±SD	73.7 ± 39.6 *	86.1 ± 10.9 **	74.8 ± 29.0 *	115.0 ± 38.4 **
		median	60.0	92.0	79.0	102.0
HDL-C (mg/dL)	M±SD	64.1 ± 20.3	65.2 ± 23.7	70.1 ± 15.1	63.0 ± 24.1	
	median	57.0	67.0	74.0	60.0	
LDL-C (mg/dL)	M±SD	114.3 ± 26.7	129.9 ± 31.2	130.1 ± 39.9	156.1 ± 38.5	
	median	110.5	132.0	136.5	155.0	
Uric Acid (mg/dL)	M±SD	5.4 ± 1.2	5.2 ± 1.6	5.6 ± 1.1	5.1 ± 1.1	
	median	5.0	5.2	5.5	5.1	

M±SD: mean±standard deviation,

Calorie Restriction (CR) diet was provided on day 1 and 2.

Low Carbohydrate Diet (LCD) was continued from day 3 to 14

ns: not significant difference compared with the value on day 2

\*: significant difference compared with the value on day 2 (p<0.05)

\*\*: significant difference compared with the value on day 2 (p<0.01)

## 2) Cases on LCD treatment

Two cases were treated on LCD and their M values were investigated 3 times, which are shown in Fig.2. Case 1 was 68 year-old male with HbA<sub>1c</sub> 10.3 %. Calculated M values were decreased from 1285 to 37.7 in 14 days. Case 2 was 64 year-old male with HbA<sub>1c</sub> 7.3 %. Calculated M values were decreased from 426 to 7.4 in 14 days.

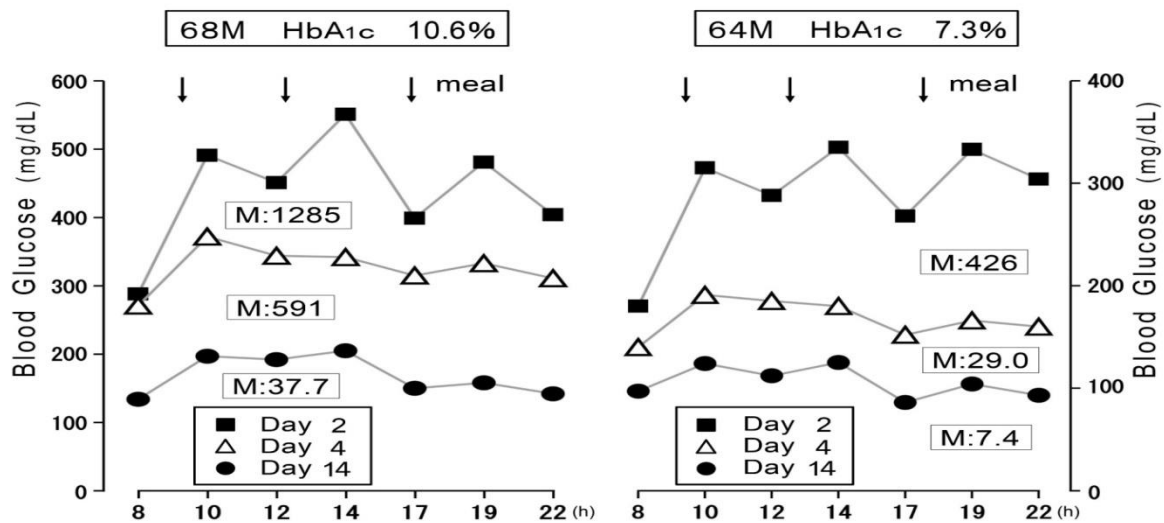


Figure 2: The changes of M value from CR to LCD

Figure 2a: 68 year-old men showed decreased M value from 1285 to 37.7 in 14 days.

Figure 2b: 64 year-old men showed decreased M value from 426 to 7.4 in 14 days.

### 3) Correlations among biomarkers on CR and LCD:

There was significant correlation between HbA1c value and M value on day 2 (Fig.3).

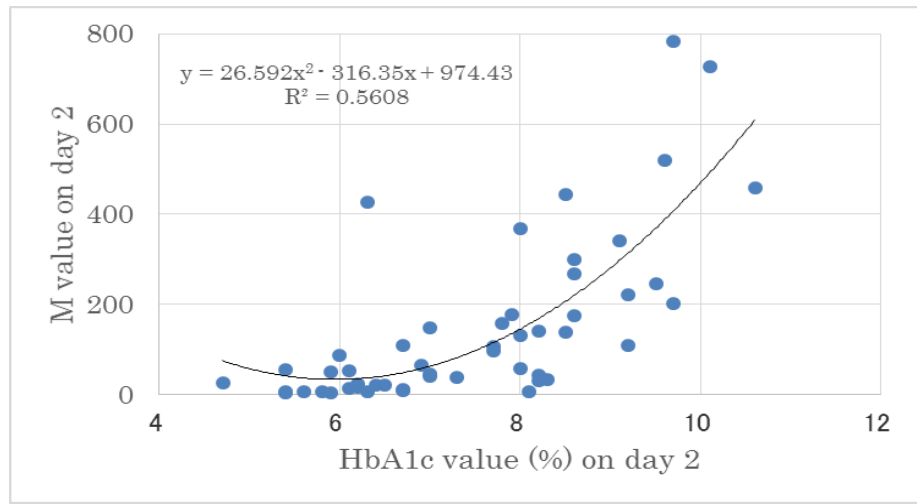


Figure 3: Correlation between HbA1c value and M value on day 2

The Changes of blood glucose and M value on CR and LCD were shown in Fig.4. There were significant correlation between average blood glucose and M value on day 2 and 4.

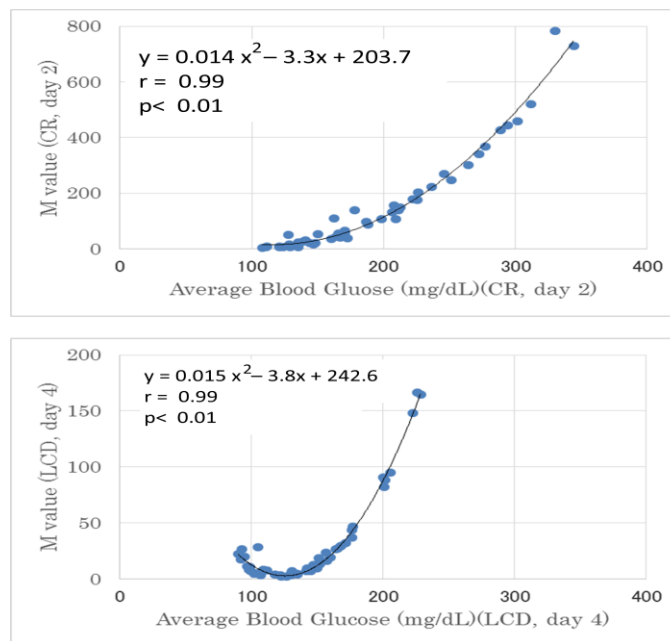


Figure 4: The Changes of blood glucose and M value on CR and LCD

Fig.4a: The correlation between average blood glucose and m value on CR (day 2)

Fig.4b: The correlation between average blood glucose and m value on LCD (day 4)

Average blood glucose between CR and LCD had significant correlation (Fig.5), in which the regression line showed  $y = 0.49x + 48.1$ . There was significant correlation of M value between CR and LCD on day 2 (CR) and day 4 (LCD), with the regression line  $y = 0.16x + 5.0$  (Fig.6).

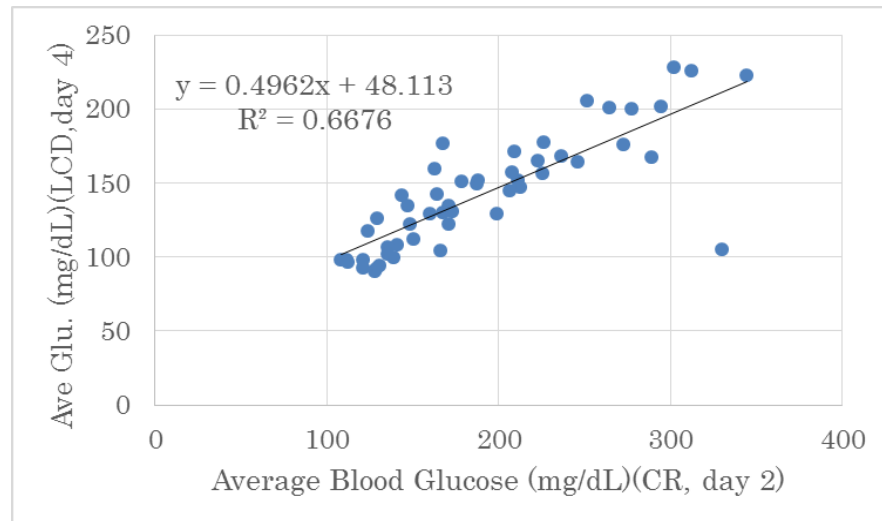


Figure 5: Correlation of average blood glucose between CR and LCD

Blood glucose was measured on day 2 (CR) and day 4 (LCD).

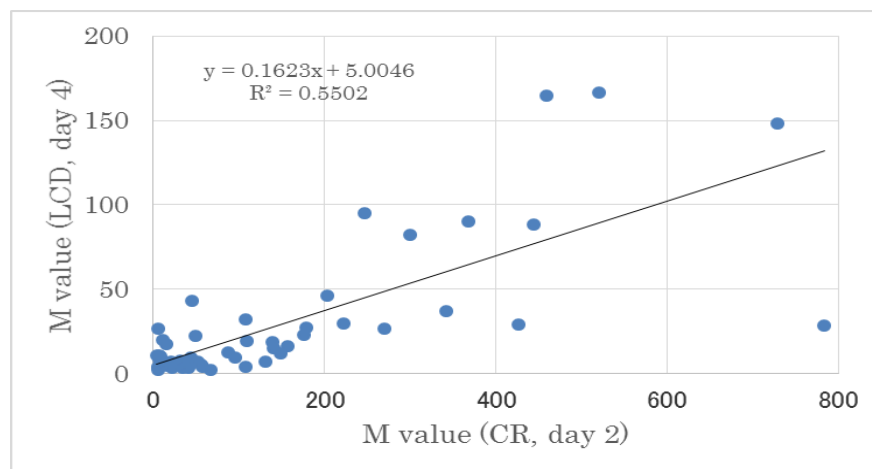


Figure 6: Correlation of M value between CR and LCD

M value was obtained each, on day 2 (CR) and day 4 (LCD).

## Discussion

Recently, oxidative stress has been one of the most valuable problems. Patients with type 2 diabetes mellitus (T2DM) always have hyperglycemia and increased mean amplitude of glycemic excursions (MAGE), which would be the highest risk for oxidative stress and for the development of complications [18].

A strong relationship between glycemic variability and oxidative stress in poorly regulated T2DM, but no relevant relationship between them in well-regulated type 2 diabetes patients [19].

Then, investigation of glucose variability and treatment for glucose profile are necessary. In this study, we will indicate the usefulness of Morbus (M) value for evaluation and management for T2DM patients.

### 1. LCD and its efficacy

LCD have been begun and prevalent by Bernstein and Atkins [20, 21]. After that, lots of studies were reported with clinical efficacy of weight reduction and improved glucose level [1-6, 22, 23]. Recently, the research of LCD have focused to less influence to cardiovascular risk factors [24-26], and to renal function [27].

One of the reason for the effect of LCD would be the elevated ketone bodies, namely, ketogenic diet [28, 29]. The author and colleagues have reported clinical application of LCD for 2699 cases [11], and investigated elevated ketone bodies on LCD and on the pregnant mother-placenta-newborn axis [10, 11], and developed LCD broadly socio-economically in Japan [30, 31].

Feinman, Bernstein and et al. stated the suggested definitions of LCD as follows [32]: 1) Very low-carbohydrate ketogenic diet (VLCKD): Carbohydrate, 20–50 g/d or <10 % of the 2000 kcal/d diet, which is recommended early phase of induction for popular diets such as Atkins Diet or Protein Power, 2) Low-carbohydrate diet: <130 g/d or <26 % total energy, which is near the American Diabetes Association (ADA) definition of 130 g/d as its recommended minimum, 3) Moderate-Carbohydrate Diet: 26 %–45 %, 4) High-Carbohydrate Diet: >45 %.

In this study, we adopted super-LCD including 12 % carbohydrate, which is equivalent to VLCKD, because of all cases with hyperketonemia. Our formula diet contains 1400 kcal/day, which has 168kcal of carbohydrate (1400 x 0.12), and 42g of carbohydrate per day [7, 11, 30].

### 2) Blood glucose variability

In current study, average blood glucose in 4 groups decreased significantly, indicating the short effect of LCD. Furthermore, simultaneously calculated M value also significantly decreased, suggesting decreased glucose level and fluctuation. M value is characterized for its larger numerical change than that of glucose, and for better evaluation of relieving status.



Study of 2 cases revealed that M values on day 14 decreased from those on day 2 and 4, in which M value would be useful for evaluating process in a case and comparing some cases.

M value correlates with glucose and HbA1c, and M value would increase when average blood glucose decrease from 100mg/dl to 80mg/dL, because M value becomes minimum when blood glucose is 100 mg/dL.

The correlation of average blood glucose between CR (day2) and LCD (day4) showed the linear regression curve,  $y = 0.49x + 48.1$ , suggesting the possible speculation of average glucose level starting LCD from CR. Similarly, the correlation of M value between day 2 and 4 showed the linear regression curve,  $y = 0.16x + 5.0$ , indicating rapid improvement of glucose level and fluctuation.

As carbohydrate rate in CR vs LCD are 60 % vs 12 %, respectively, with the same calorie of 1,400 kcal/day, the carbohydrate dose of CR and LCD would be 210g vs 42g per day, which was one-fifth, namely, approximately 0.2. Taking both data 0.16 and 0.2 into consideration, M value could possibly predict carbohydrate intake amount.

There are rare reports concerning Morbus value. Patients with T1DM (n=29) were investigated for blood glucose fluctuations 3 times and more per day, using continuous glucose monitoring (CGM) and self-monitoring of blood glucose (SMBG) [33]. Consequently, our results would become the fundamental data for carbohydrate intake and blood glucose variability in the light of M value.

### 3) Morbus value

Daily glucose profile can be calculated into MAGE [13] and M (Morbus) values [12], and the latter would be more practical. M value is characterized for its points. The optimal blood glucose is set at 0 as the standard, then M value increases when average blood glucose changes from 100mg/dl to 90 mg/dL. As to sampling frequency, there were similar results on 7 times and 20 times per day [12, 15, 17]. It also showed similar result in comparison with continuous glucose monitoring (CGM) measurement for 48 hours which is ideal research method [34, 35].

In addition to M value, further investigation is possible for glucose variability, which are the mean amplitude of glycemic excursions (MAGE), standard deviation (SD), the mean of the daily difference (MODD) through continuous glucose monitoring (CGM) [15, 36-38].

### 4) LCD and future study

As T2DM patients are increasing, management and treatment for them will be improved according to adequate guideline and efficacy of reports [39, 40].

In this study, we discussed CR and LCD. However, there are several kinds of well-known nutritional diet methods. Different dietary approaches on glycemic control will be in research in the future, including 9 kinds of diet, namely,

Control, low-carbohydrate, low-fat, Mediterranean, High-protein, vegetarian, DASH, Paleo, low-glycemic index/load [40, 41].

As to research development for glucose variability, several markers would be involved together such as M value, MAGE, HbA1c, average blood glucose and diabetic complication [42]. Moreover, nutritional research will possibly apply new scoring system, such as Nutri Grade, which will develop diabetic practice and research in the future [43].

### **Conclusion**

In this study, the changes and significance of M value was investigated from CR to LCD in patients with T2DM. The efficacy of LCD was observed from day 2 to day 4, with significant decrease in glucose and M value, which is due to decreased carbohydrate amount from 210g (CR) to 42g (LCD) per day. There were significant correlations among several biomarkers. These findings suggest that M-value would be useful marker for clinical treatment of T2DM and research development in glucose variability.

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### **Conflicts of Interest**

The authors declare that they have no conflicts of interest.

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