Difference of Glucose variability between Low Carbohydrate Diet (LCD) and Calorie Restriction (CR)

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Abstract

Background: There have been lots of discussion and controversy concerning the difference between Low Carbohydrate Diet (LCD) and Calorie Restriction (CR). The important points include glucose variability, glucose-lowering effect, weight reduction degree and influence on lipid metabolism.

Subjects and Methods: Enrolled subjects were 47 patients with T2DM. Methods included the study for providing subjects CR meal with 60% carbohydrate on day 1-2 and LCD meal with 12% on day 3-14. Daily profile of blood glucose was studied seven times a day on day 2 and day 4. Further, biomarkers including HbA1c, average blood glucose, and M value were investigated and analyzed for mutual correlations.

Results: Subjects were categorized into 4 groups according to the average glucose value, which were 124mg/dL, 160mg/dL, 206mg/dL, and 281mg/dL, respectively. Data in 4 groups were as follows: Number; 12,12,12,11, Male/Female; 6/6, 3/9, 6/6, 5/6, mean age; 51.3, 60.9, 65.3, 60.6 years old, HbA1c; 6.1%, 7.1%, 8.0%, 8.9%, fasting glucose on day 2; 109 mg/dL, 136 mg/dL, 178 mg/dL, 224mg/dL, respectively. Daily profiles of blood glucose in 4 groups on day 4 were remarkably decreased than those of day 2. The levels of M value indicating average blood glucose and mean amplitude of glycemic excursions (MAGE) on day 2 vs 4 were compared in 4 groups, which are 7.1 vs 10.5, 39.7 vs 5.0, 139 vs 15.7, 367 vs88, respectively. Correlations among HbA1c, M value and average blood glucose showed significant correlations (p<0.01).

Discussion and Conclusion: Obtained results showed that the distribution of daily profile of blood glucose in 4 groups is separated. Further similar tendency was observed in HbA1c and M value.

There was remarkable decrease of blood glucose from CR to LCD. These findings suggested that LCD would have remarkable efficacy for improving glucose variability. Furthermore, obtained findings could become basal and reference data for the developing research for CR and LCD.

Key words:

Glucose variability; Type 2 diabetes mellitus (T2DM); Low Carbohydrate Diet (LCD); Morbus value (M value); Calorie Restriction (CR)

Abbreviation:

LCD: Low Carbohydrate Diet; T2DM: Type 2 diabetes mellitus; CR: Calorie Restriction; IRI: Immunoreactive Insulin; M value: Morbus value; HOMA-R: Homeostasis Model Assessment of Insulin Resistance; HOMA-β: Homeostasis Model Assessment of β Cell Function.

Introduction

Diabetes has been increasing, and about 451 million people with diabetes are estimated to be present worldwide in 2017 [1]. The number will be expected to increase to 693 million by 2045. Among the people who are estimated to have diabetes at present, almost half of people with diabetes are not diagnosed yet. Thus, it is crucial to deal with diabetes medically and socially [2].

With regard to the diagnosis and treatment for diabetes, there have been controversies in several diabetes societies [3,4]. There have been some discussions about the recommended level of HbA1c that would be the goal for clinical management for diabetes, between the **American Diabetes Association** (ADA) and the **American College of Physicians** (ACP) in recent years [4,5]. From the clinical point of view, there have been diabetic variability with various heterogeneity. Then, we have to argue the adequate control situation in each diabetic patient [5,6].

The basal treatment for diabetes has been nutritional therapy. The basal treatment for diabetes has been diet therapy, which is one of the three main treatment for diabetes including i) diet therapy, ii) exercise therapy, iii) anti-diabetic agents or insulin for medicine. As to the diet therapy for diabetes, there have been discussions about **Calorie Restriction** (CR) and **Low Carbohydrate Diet** (LCD) which are categorized into two major nutritional characteristics nutrition's. Bernstein et al. has begun to present LCD in 1990' and applied LCD for the treatment of diabetes [7].

In succession, the report from the **Dietary Intervention Randomized Controlled Trial** (DIRECT) Group has been known widely [8]. They compared LCD, CR (Low-Fat Diet) and the Mediterranean diet, with the result of the predominance of LCD for 2 years. After that, the efficacy of LCD for 4 years of interventions was reported [9].

In contrast, authors and co-researchers have initiated LCD in Japan [10]. After that, we have developed the clinical efficacy of LCD through educational books and workshop for long [11]. Recently, Japan LCD promotion association has been established and its activities have continued [12]. We have also continued clinical research of LCD and CR and reported the significance and pathophysiological role of **Ketone Bodies (KB)** in the circumstances of the axis of fetus-placenta-newborn-mother [13]. For patients with diabetes and Met-S and general people, we have presented three types of recommending LCD meals, such as super LCD, moderate LCD and petite LCD meals [14].

In this study, authors and colleagues have presented the comparison with CR meal and LCD meals for diabetic patients. Further, diabetic biomarkers including HbA1c, M value, lipids were investigated for mutual correlations for clarifying the pathophysiology and glucose variability in diabetes.

Subjects and Methods

In this study, the enrolled subjects were 47 patients, who were recently diagnosed as **Type 2 Diabetes Mellitus** (T2DM). They were admitted to the hospital for further evaluation and treatment of diabetes. Especially, the purpose of the educational admission method is to understand two types of meal. During staying in the hospital, they have an experience of taking calorie restriction (CR) and also low carbohydrate diet (LCD), consecutively. For this series of nutritional education, they understand what are CR and LCD like, and have the fundamental knowledge and practice for diabetes mellitus.

As to the detail of the methods, our research group has made our common diabetic formula protocol. It includes the diagnosis, examination, and treatment of the diabetic research program. The principle and the detail are as follows:

i) Concerning the diagnosis, the subjects in this study were diagnosed as T2DM in the recent period. We excluded specific types of diabetes, including type 1 diabetes mellitus (T1DM) or others. These patients with T2DM were not administered medicine for diabetes, which can influence glucose variability in daily profile and also postprandial glucose response.

ii) The protocol included 14 days of further evaluation and treatment for T2DM. They were admitted in the hospital and were given several examinations. On the next day of the admission, which is day 2, they were drawn blood samples for fundamental examination after overnight fasting. The exams included complete blood count, renal and liver function test, lipids, and etc. Regarding examination items for diabetes, we ordered blood glucose level on fasting and postprandial time, as well as Immunoreactivity of Insulin (IRI), HbA1c, C-peptide, HOMA-R, HOMA-β, M value were obtained for the study.

iii) In our protocol, nutritional therapy includes two kinds of diet. CR meal was provided in day 1 and 2 which has 1400 kcal/day with the PFC ratio as 15: 25: 60. This has been the standard Japanese meal pattern recommended by the Japan Diabetes Association (JDA) [15].

iv) Successively, LCD meal was provided during day 3 to day 14. It has a 1400kcal/day with the PFC ratio from day 3 to 14 with super LCD. The content has 12% of carbohydrate with 1400 kcal/day with 12% of carbohydrate ratio. This has been called as super-LCD, which has been well-known and popular in Japan. In our protocol, there are three types of LCD meals, which are super LCD, standard LCD with 26% of carbohydrate and petite LCD with 40% of carbohydrate.

v) Research protocol included the comparison of the values in several biomarkers between day 2 and day 4, and between day 2 and day 14. The former included the comparison of CR and LCD meals on day 2 and day 4. The latter included the comparison of lipids such as triglyceride, HDL-cholesterol and LDL-cholesterol.

Glucose profile:

In order to clarify the daily profile of blood glucose, we measured blood glucose 7 times from morning until night. The times were 0800, 1000, 1200, 1400, 1700, 1900 and 2200h. CR meal was given on day 1 and day 2, and a daily profile of blood glucose was studied on day 2. Similarly, LCD meal was given during day 3 and 14, and a daily profile of blood glucose was studied on day 4. Glucose variability was investigated between day 2 and day 4. According to the obtained data of blood glucose 7 times a day, blood glucose in average and M value were calculated by the calculation equation of the formula on M value [16, 17].

M value:

It is M value that has been evaluated as one of the useful biomarkers for glucose variability. M value shows two valuable meaningful data. The former means the value of the average blood glucose per day, and the latter means the width of the glucose fluctuation, which reveals the **Mean Amplitude of Glycemic Excursions (MAGE)** [18-20]. Both data obtained can

speculate the general glucose variability in a day.

Thus, M value can be revealed as a numerical value which includes two valuable markers. One is the degree of elevated blood glucose in average, and another is the increased swinging of the variability of blood glucose. By applying the mathematics method, we can calculate M value as the equation of the logarithmic transformation. As to the significance of M value, it means the degree of the glucose deviation from the ideal blood glucose profile in a day [19-21].

The calculation way for the M value includes three processes. The first one shows the basal equation, which is $M = M^{BS} + M^{W}$. M value means the total value of both M^{BS} and M^{W}. The second shows the M^{W}, that expresses (maximum blood glucose − minimum glucose)/20. The last one revealed that M^{BS} is the mean of MBSBS. Summarizing these into one equation, MBSBS has been the individual M-value for each blood glucose, which is calculated as (absolute value of $[10 \times \log (\text{blood glucose level}/120)])^{3}$ [19-21].

Generally, there has been clinically estimation of judgment for glucose variability from the elevated level of M value. For the result of M value, the standard normal range has been less than 180, and the borderline is 180 and more than 180 and less than 320, and the abnormal range is 320 and more than 320.

Ethical Considerations:

This study has been fundamentally performed in compliance with the ethical principles based on the Declaration of Helsinki. Moreover, the additional commentary was conducted on the Ethical Guidelines for Research in the medical field for Humans and in accordance with the Good Clinical Practice (GCP). They were found associated with the ongoing consideration for the protection of human rights. Further, "Ethical Guidelines for Epidemiology Research" was applied as an adequate guideline. It was presented in Japan by the Ministry of Education, Culture, Sports, Science, and Technology and the Ministry of Health, Labor and Welfare.

The author and our researchers have established an ethical committee. As regard to the discussion for the medical and ethical problems, included professions were a medical doctor, nurse, pharmacist, nutritionist and other experts in the legal specialty. For the current investigation, our discussion resulted in appropriate and valid, with the agreements. From the point of patients' view, the informed consents and written document agreements have been obtained from all the subjects. Current investigation has been registered by the National University Hospital Council of Japan (ID: #R000031211).

Results

Fundamental data:

In the current study, 47 patients with T2DM were enrolled and their fundamental data of several biomarkers were shown in **Table-1**. Average ages in 4 groups were from 51.3 to 65.3 years old, and the number of male/female was 20 / 27, respectively. The grouping was performed by the level of average blood glucose, which were 124mg/dL, 160mg/dL, 206mg/dL, 281mg/dL, respectively. HbA1c value in 4 groups was 6.1, 7.1, 8.0 and 8.9%, respectively.
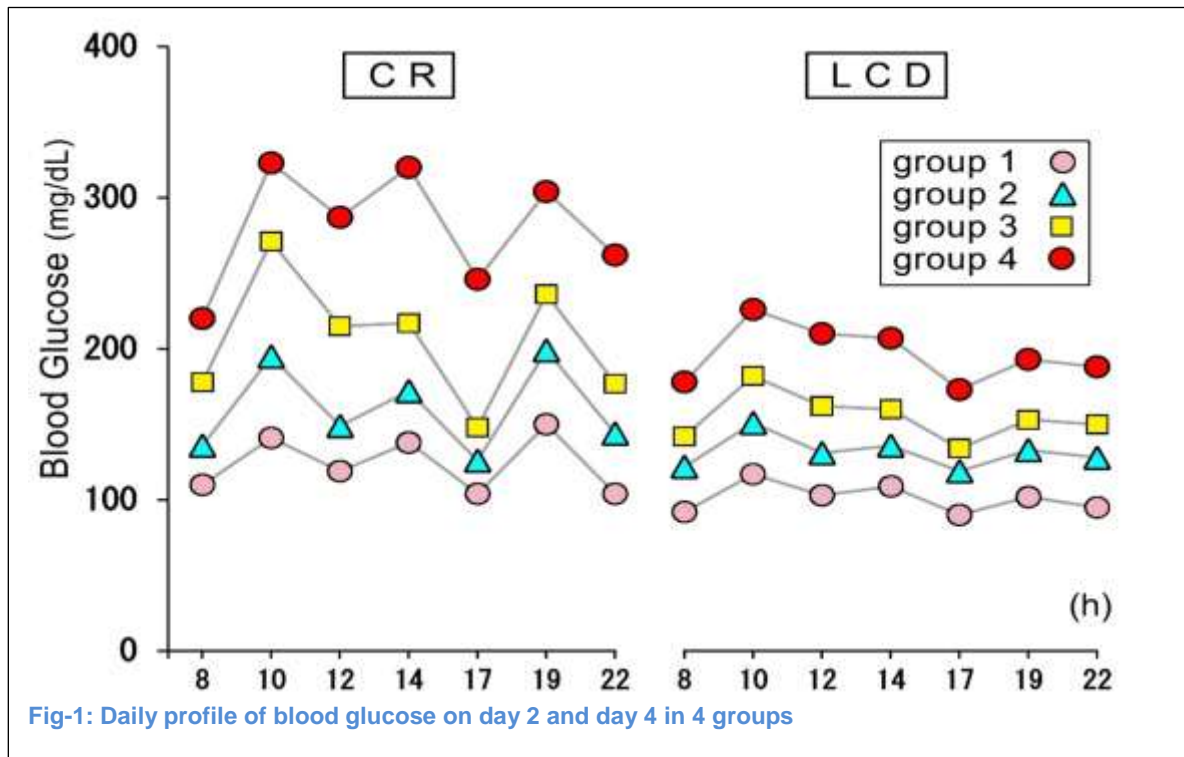
The average blood glucose 2 hours after breakfast on day 2 vs day 4 in 4 groups were as follows: 141.6 vs 116.6 mg/dL, 194.8 vs 151.2 mg/dL, 271.3 vs 181.8 mg/dL and 323.0 vs 226.0 mg/dL, respectively.

The median value of the immunoreactivity of insulin (IRI) on fasting in each group was 6.7, 7.5, 4.1 and 5.6μU/mL respectively. The value of HOMA-β in each group was 76.5, 29.3, 21.3 and 11.8, respectively. The median value of triglyceride on fasting on day 2 vs day 14 in 4 groups were as follows: 120 vs 73 mg/dL, 107 vs 86 mg/dL, 116 vs 85 mg/dL and 190 vs 124 mg/dL, respectively.

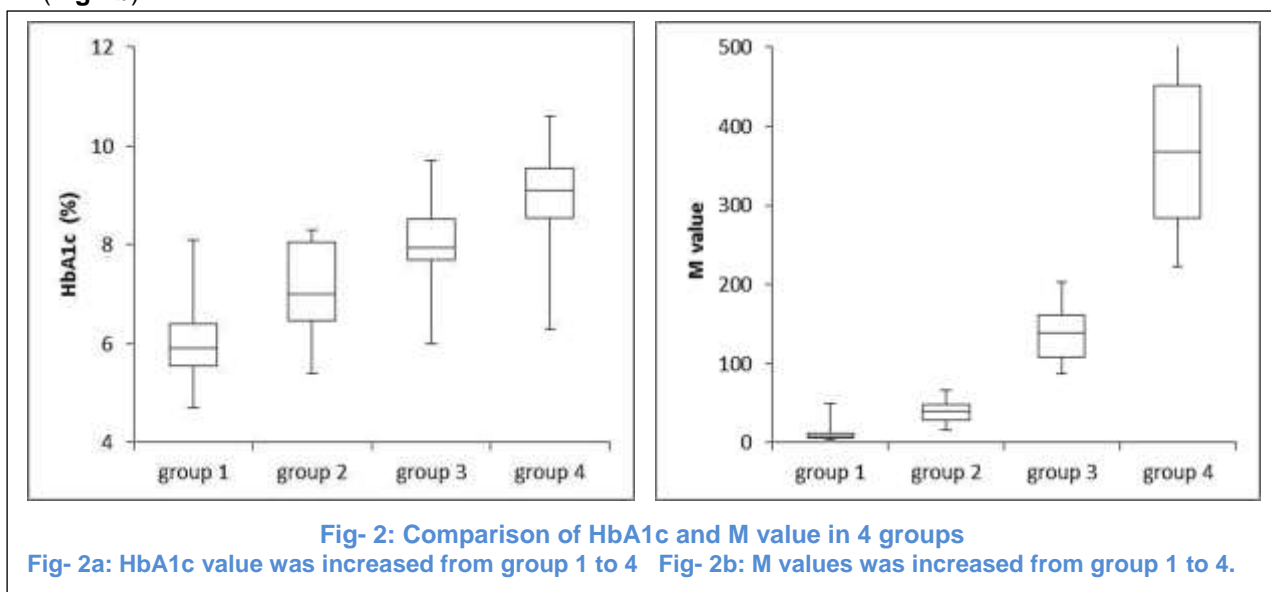| Table-1: Biomarkers in the subjects classified for 4 groups					
Group		**Group 1**	**Group 2**	**Group 3**	**Group 4**
Subjects	Number	12	12	12	11
	Sex (male/female)	6/6	3/9	6/6	5/6
	Age (years old.)	51.3 ± 13.1	60.9 ± 16.5	65.3 ± 8.7	60.6 ± 5.7
Glucose	HbA1c (%)	6.1 ± 0.9	7.1 ± 0.9	8.0 ± 1.0	8.9 ± 1.2
	Glucose (0) on day 2 (mg/dL)	109.2 ± 16.2	135.5 ± 18.1	177.7 ± 36.3	220.4 ± 29.5
	Glucose (120) on day 2 (mg/dL)	141.4 ± 32.0	194.8 ± 34.9	271.3 ± 36.5	323.0 ± 45.0
	Glucose (0) on day 4 (mg/dL)	91.7 ± 15.4	122.1 ± 14.3	142.2 ± 19.3	177.6 ± 22.0
	Glucose (120) on day 4 (mg/dL)	116.6 ± 15.4	151.2 ± 15.3	181.8 ± 17.6	226.0 ± 29.4
Resistance	Insulin (0) on day 2 (µU/mL)	6.7 [2.6 - 11.7]	7.5 [3.9 - 9.5]	4.1 [3.5 - 9.0]	5.6 [3.3 - 7.3]
	HOMA-R	2.2 [0.7 - 3.3]	2.3 [1.2 - 3.3]	2.1 [1.2 - 3.9]	3,0 [1.9 - 4.3]
	HOMA-β	76.5 [24.1 - 83.1]	29.3 [19.7 - 50.3]	21.3 [10.2 - 29.7]	11.8 [7.6 - 16.6]
Lipids	Triglyceride on day 2 (mg/dL)	120 [69 - 155]	107 [77 - 126]	116 [77 - 134]	190 [169 - 257]
	Triglyceride on day 14 (mg/dL)	73 [57 - 103]	86 [75 - 94]	85 [58 - 107]	124 [95 - 152]
	HDL-Chol on day 2 (mg/dL)	57 [51 - 75]	50 [47 - 67]	74 [65 - 78]	60 [44 - 73]
	HDL-Chol on day 14 (mg/dL)	48 [44 - 61]	47 [43 - 64]	60 [46 - 74]	46 [41 - 65]
	LDL-Chol on day 2 (mg/dL)	120 [106 - 147]	115 [84 - 134]	151 [112 - 164]	155 [141 - 186]
	LDL-Chol on day 14 (mg/dL)	133 [113 - 153]	136 [118 - 165]	136 [122 - 152]	179 [142 - 199]
The results were expressed by mean ± SD or median [25% - 75%].					

Daily profile of blood glucose:

   Daily profile of blood glucose in 4 groups was investigated (**Fig-1**). Blood glucose variability in 4 groups showed the parallel pattern. Among them, blood glucose value is the lowest in group 1 and is the highest in group 4. Acute elevation of blood glucose was observed from 0800h to 1000h on the morning of day 2. The evaluation degree became smaller on day 4 compared with that of day 2.

Fig-1: Daily profile of blood glucose on day 2 and day 4 in 4 groups
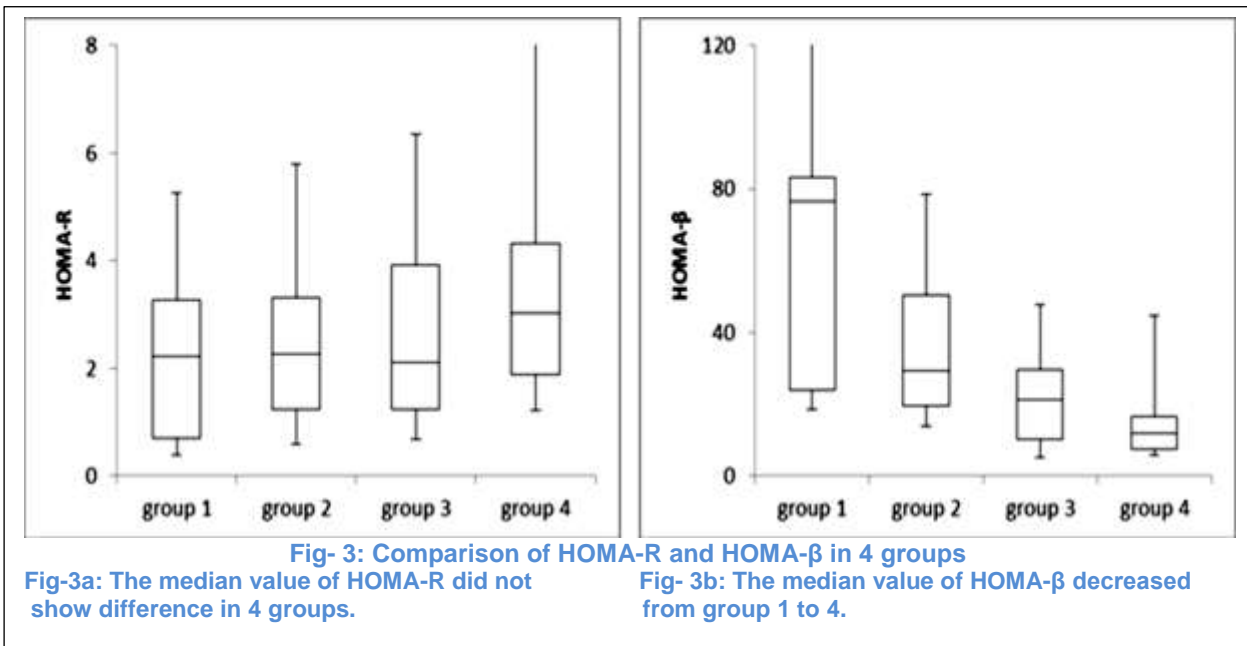
HbA1c and M value:

   Comparison of HbA1c and M value in 4 groups are shown in **Fig-2**. The median value of HbA1c was increased from group 1 to 4 (**Fig-2a**). Obtained data of M value was increased from group 1 to 4 (**Fig-2b**).

Fig- 2: Comparison of HbA1c and M value in 4 groups
Fig- 2a: HbA1c value was increased from group 1 to 4   Fig- 2b: M values was increased from group 1 to 4.

Regarding median values in groups 1 to 4, a linear increase was observed in HbA1c and a sharp increase in M value which is like a quadratic curve.
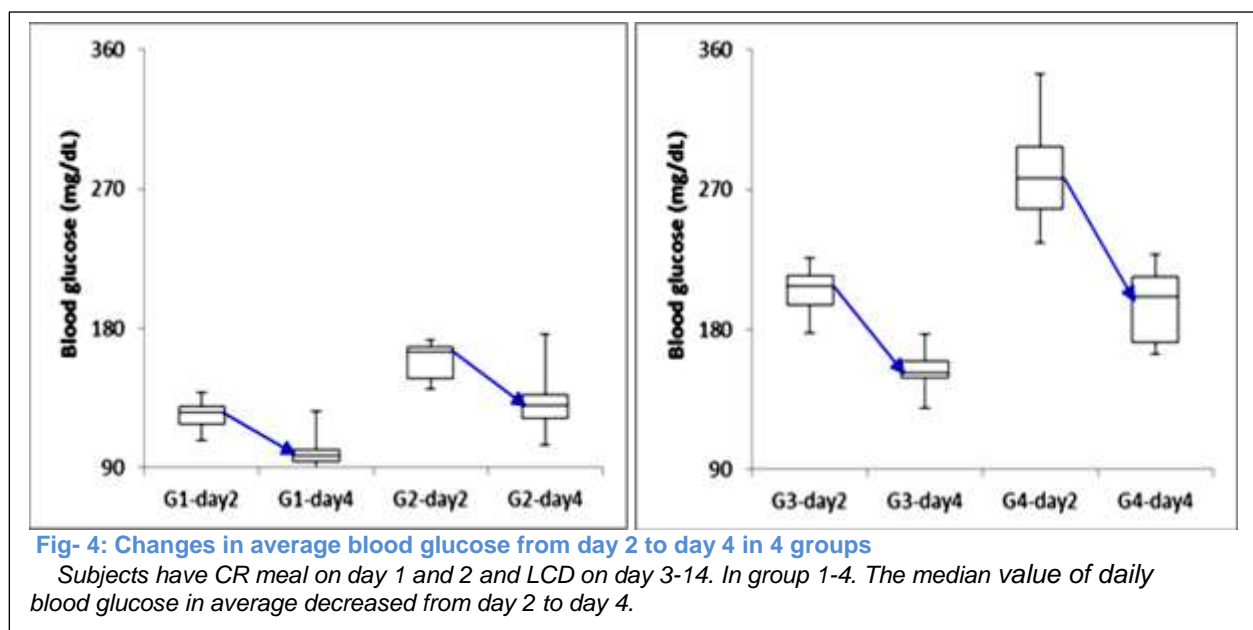
HOMA-R and HOMA-β:

Comparison of HOMA-R and HOMA-β in 4 groups is shown in **Fig-3**. The median value of HOMA-R did not show the difference in 4 groups (**Fig-3a**). In contrast, the median value of HOMA-β decreased from group 1 to 4 with a remarkable degree (**Fig-3b**).

Fig- 3: Comparison of HOMA-R and HOMA-β in 4 groups

Fig-3a: The median value of HOMA-R did not show difference in 4 groups.   **Fig- 3b: The median value of HOMA-β decreased from group 1 to 4.**

Changes in average blood glucose:

Changes in average blood glucose from day 2 to day 4 in 4 groups were shown in **Fig-4**. Subjects have CR meal on day 1 and 2, and LCD meal on day 3-14. In group 1-4, the median value of daily blood glucose in average decreased from day 2 to day 4.

Fig- 4: Changes in average blood glucose from day 2 to day 4 in 4 groups
   Subjects have CR meal on day 1 and 2 and LCD on day 3-14. In group 1-4. The median value of daily blood glucose in average decreased from day 2 to day 4.

Comparison on day 2 vs day 4:

The levels of M value on day 2 vs day 4 were compared in 4 groups (**Fig-5**). The median value in each group was 7.1 vs 10.5, 39.7 vs 5.0, 139 vs 15.7, 367 vs88, respectively. In group 1, the data of M value was not changed. In group 2, 3, and 4, there was a remarkable decrease of M value for 2 days.
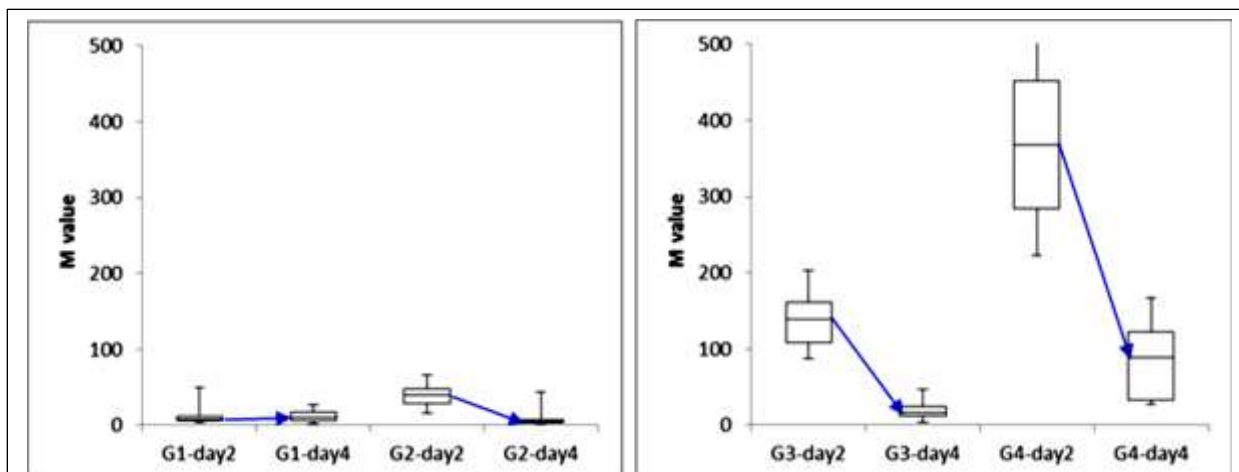

Fig 5: Changes in M value from day 2 to day 4 in 4 groups
Subjects have CR meal on day 1 and 2 and LCD on day 3-14. In group 1-4. M value decreased in 4 groups from day 2 to day 4.

Correlation among biomarkers:

Correlations of biomarkers among HbA1c, M value, and average blood glucose were shown in **Fig-6**. There are significant correlations between HbA1c and average blood glucose on day 2 ($p<0.01$), and between HbA1c and M value on day 2 ($p<0.01$).
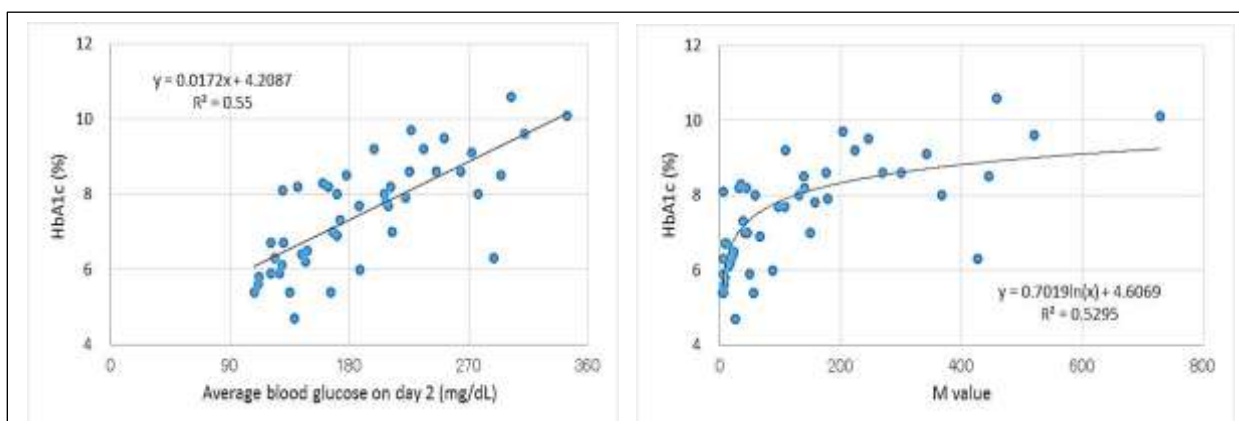

Fig- 6: Correlations of biomarkers HbA1c, M value and average blood glucose.
There are significant correlations between HbA1c and average blood glucose on day 2 (p<0.01), and between HbA1c and M value on day 2 (p<0.01).

Correlation between day 2 and 4:

Correlations of the value of day 2 and day 4 in M value and in average blood glucose were shown in **Fig-7**. There are significant correlations between the value of 2 and day 4 in average blood glucose ($p<0.01$), and in M value ($p<0.01$).
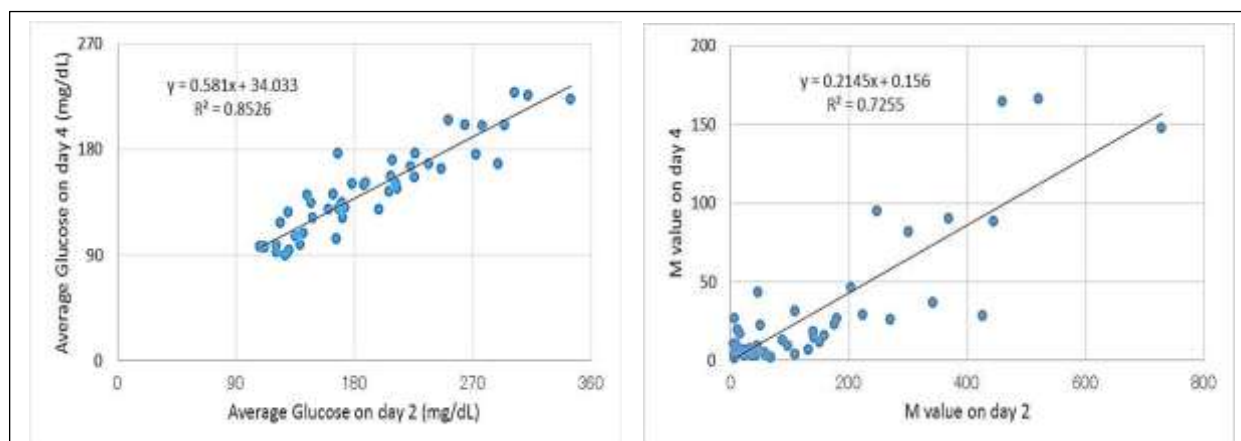
Fig- 7: Correlations of the value of day 2 and day 4 in M value and in average blood glucose.
There are significant correlations between the value of day 2 and day 4 in average blood glucose ($p<0.01$), and in M value.

Discussion

Regarding nutritional therapy for diabetes mellitus, clinical research for CR and LCD have been found for years [11,14,23]. For the development of LCD medically and socially, three types of LCD meals have been presented. They are super LCD, standard LCD, and petite LCD, which are including carbohydrate as the ratio of 12%, 26% and 40%, respectively [12,14]. Actually, the type of LCD used in this study was super-LCD, which has evaluated as an effective LCD meal for obesity and diabetes [24, 25].

In the current study, glycemic variability on CR and LCD were measured and investigated. As to our protocol, we have had experiences of clinical research using CR meal and LCD meal [26]. By combined data of daily profile of blood glucose, HbA1c, M value, a pathophysiological aspect of precise glucose variability would be clarified. The results of this study are obtained in Figures, which will be discussed in this order.

The attributes of the subjects in the 4 groups were not remarkably different. As a result of categorizing to 4 groups with mean blood glucose, the mean HbA1c and median M value seemed to be reasonable. On day 2 and 14, the TG value was remarkably decreased, which was the same tendency as previously reported [25,27]. On the other hand, there were no obvious changes in HDL and LDL.

Meals administered to the subjects were CR on days 1-2 and LCD on days 3-14. Only 24 hours after changing to LCD, glucose profile on day 4 was studied. Pre-prandial blood glucose levels on 0800h, 1200h and 1700h were decreased dramatically on day 4 in comparison with those on day 2. Furthermore, postprandial blood glucose elevation on 1000h, 1400h, and 1900h was remarkably suppressed. Consequently, these changes seem to be clinically obvious effects of LCD.

The median values of HbA1c and M value increased similarly for groups 1 to 4. As to HbA1c, the overlapping area in each group was broad, whereas in M value there were few overlapping regions and the distribution was rather distant from each other. This is one of the characteristic features of M value [28]. When the level of blood glucose and MAGE become higher, the M value will increase remarkably. Therefore, M value seems to be clinically useful when we evaluate the glycemic variability. In other words, we can compare the difference between the diabetic cases, and also the difference of clinical course for a certain diabetic patient.

HOMA is an index calculated from the ratio of blood glucose level and insulin value [29]. There are two biomarkers, in which HOMA-R is related to insulin resistance and HOMA-β is deeply related to insulin secretion ability [30]. From the results of this study, it is suggested that there

may be a decrease in insulin secretion ability for groups 1 to 4.

As to 4 groups, when comparing the average blood glucose on day 2 and 4, the apparent decrease was observed for 24 hours. The extent of the decrease was found small to larger in the order of the group 1 to 4. In particular, group 4 showed a remarkable decrease in median average blood glucose level from 277 mg / dL to 201 mg / dL for 48 hours apart. As described above, LCD has clinically a hypoglycemic effect. As the initial blood glucose level is higher, there seems to be a tendency with larger decreasing effect.

For comparison of day 2 vs day 4, mean blood glucose remarkably decreased in group 1-4. However, M value in group 1 did not show a decline. The reason would be that the M value becomes the minimum level when the blood glucose is around 120 mg/dL, indicating almost zero [31]. Therefore, the mean blood glucose level decreased in group 1, while the M value did not show a decrease. On the other hand, M value in group 3,4 decreased remarkably on day 4 than that of day 2. Compared to the decrease in mean blood glucose, the decrease of M value seems to be very to large extent. This is a beneficial point of M value, indicating both the mean blood sugar and **mean amplitude of glycemic excursions** (MAGE) [32]. Thus, M value would be useful in the comparative study.

There was a significant correlation between HbA1c and mean blood glucose on day 2, with a high correlation coefficient as $R^2 = 0.55$. The obtained formula was $y = 0.0172 x + 4.2087$. Meanwhile, the standard formula reported by Nathan et al. has been known, which is average blood glucose level (mg / dL) = 28.7 x A1 c (%) - 46.7 [33].

Here, both formulas would be compared and calculated. For example, 3 cases are tried where the average blood glucose is 120 mg/dL, 150 mg/dL, 180 mg/dL. Our formula showed HbA1c = 6.2%, 6.8%, 7.3%, respectively, and Nathan's formula showed HbA1c = 5.8%, 6.8%, 7.8%,

respectively. Both indicated the same value of HbA1c when the blood glucose is 150 mg/dL. Regarding the inclination of the HbA1c change, it is smaller in our equation and larger in Nathan's equation.

One reason would be the difference in the subjects. Our study covers 47 T2DM patients with a rather limited study. In contrast, Nathan et al. included thousands of normal individuals, diabetic patients with mild to severe range of subjects. It is inferred that the differences would be from this distribution difference in both.

There were significant correlations between HbA1c and M value on day 2 (p<0.01). The correlated pattern was not linear, but logarithmic distribution. Its characteristic points were rather different in each level as follows: i) M value is rather low when HbA1c is about 5.0 – 7.0 %, ii) it increases abruptly when HbA1c is 7.0% - 8.0 %, iii) it is widely distributed when HbA1c is more than 8.0% [34]. From these findings, diabetic cases with HbA1c value of more than 8.0% probably show wider glucose variability with average glucose and MAGE.

The average blood glucose between Day 2 and Day 4 showed a high correlation coefficient with $R^2 = 0.85$. The equation was $y = 0.58 x + 34.0$, and we can speculate the average blood glucose of day 4 from the data on day 2. If the average blood glucose is 270 mg/dl on day 2, the estimated value on day 4 is 191 mg/dL. If it is 180mg/dL on day 2, it would 138 mg/dL on day 4. Thus, the clinical effect of LCD can develop research possibility [25, 35].

Moreover, there was significant correlation of M value between Day 2 and Day 4 (p<0.01), with the equation as $y = 0.21 x + 0.16$, and $R^2 = 0.73$. It showed the rapid decrease of M value for only 2 days. This may be due to a sharp improvement in MAGE as well as decreased mean blood glucose. As described above, this effect is found only two days after the meal change from CR to LCD. Thus, the efficacy of LCD would be clinically remarkable in the light of glucose variability.

Conclusion

In summary, 47 patients with T2DM were studied in the current report. We investigated diabetes-related biomarkers such as HbA1c, blood glucose, IRI, HOMA-R, HOMA-β, M value and lipids, and mutual correlations among them. Daily blood glucose on LCD showed decreased level compared with that of CR. Several significant correlations were found among diabetes-related biomarkers. These results suggest that LCD would be an effective nutritional therapy for improving glucose variability and that obtained findings would become a basal reference for future research development in this field.

Acknowledgment

Conflicts Of Interest

The authors state that we do not have any conflicts of interest in this report.

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