

Improved Glucose Variability by Low Carbohydrate Diet in Female Diabetic Patients

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Abstract

Background: Discussion of Low Carbohydrate Diet (LCD) and Calorie Restriction (CR) has been observed. Authors have continued clinical research on LCD, CR and Morbus (M) value for years.

Subjects and Methods: Subjects were 81 female patients with type 2 diabetes mellitus (T2DM). Methods included i) basal tests on diabetes, ii) daily profile of blood glucose, average glucose, M value for CR meal, iii) same exam of ii) for 2 days of LCD, iv) Triglyceride check for 12 days of LCD, v) analyses of these biomarkers.

Results: Obtained data were as follows: average age 62.4 years old, median values are HbA1c 7.2%, fasting glucose 147 mg/dL, IRI 6.8 μ U/mL, HOMA-R 2.5, HOMA- β 28.7, respectively. Median values on day 2 vs 14: average glucose 173 vs 130 mg/dL, M value 62.4 vs 9.6, respectively. There was significant correlations between M value and HbA1c ($p < 0.01$), and between average glucose and HbA1c ($p < 0.01$). Triglyceride value was decreased for 12 days of LCD from 103 to 79 mg/dL.

Discussion and Conclusion: The results suggested that LCD showed positive effects for improving glucose variability and lipid metabolism. Furthermore, these findings would become fundamental and reference data for the future research development in this field.

Keywords: Glucose variability; Morbus value (M value); Low carbohydrate diet (LCD); Triglyceride (TG); Type 2 diabetes mellitus (T2DM)

1. Abbreviation

- LCD: Low Carbohydrate Diet
- T2DM: Type 2 diabetes mellitus
- IRI: Immunoreactive insulin
- M value: Morbus value
- HOMA-R: Homeostasis model assessment of insulin resistance
- HOMA- β : Homeostasis model assessment of β cell function

2. Introduction

Diabetes has been a crucial problem for years in developed countries and also developing countries. It is not only medical matter, but also social and economic matters [1]. As there have been various problems of diabetes, adequate treatment and management would be necessary in diabetic cure and care. Especially, diabetic nutritional therapy would be the important and fundamental in the clinical practice.

From the basic medical point of view, the main cause of diabetic complications are from persisting elevated blood glucose and fluctuation of glucose [2,3]. As to microvascular complications, there seemed to be several probable mechanisms influencing the biochemical changes. They may include some possibility, such as the formation of advanced glycation end products (AGEs), increased flux of glucose and other sugars through the polyol pathway, activation of protein kinase C (PKC) isoforms and increased flux through the hexosamine pathway [4,5].

From the clinical practice, management for diabetes has been on discussion concerning diagnosis and treatment. Recently, there has been controversy on discussion concerning the recommended HbA1c in American College of Physicians (ACP), American Diabetes Association (ADA) and International Diabetes Federation (IDF) [6-8]. Thus, applicable control of diabetic variability has been important to be argued [9].

Adequate nutritional therapy has been the fundamental treatment for diabetes and Metabolic syndrome (Met-S). The method of Calorie Restriction (CR) has been the main principle for diet therapy widely, but in 1990' Bernstein et al. started to apply Low Carbohydrate Diet (LCD) [10]. The efficacy of LCD for weight reduction and glucose lowering has been reported and recognized so far. After that, Shai et al. showed the data of the comparison of the efficacy of LCD, Mediterranean, Low-Fat Diet [11,12]. Various discussion between CR and LCD has been continued for long years [13,14].

On the other hand, authors and colleagues in Japan have introduced and developed LCD in Japan for long years [15]. We have continued and developed LCD movement in various axes, including educational seminars, medical journals and books and presenting in medical society [16].

We have also reported the pathophysiological role of Ketone Bodies (KB) in the circumstances of fetus, placenta, newborn and mother [17]. In addition, we have developed the prevalence of LCD by continuing the activity of Japan LCD promotion association [18]. We have recommended simple way of LCD in 3 types, which are super LCD, moderate LCD and petite LCD meals [19].

In current investigation, we compared the glucose variability on CR diet and LCD, and calculated the difference of average blood glucose and Morbus (M) value.

Moreover, we study the detail comparison and correlations among several biomarkers, such as HbA1c, glucose, lipid profile, homeostasis model assessment of insulin resistance (HOMA-R) and homeostasis model assessment of β cell function (HOMA- β).

3. Subjects and Methods

Current study enrolled 81 female patients with Type 2 Diabetes Mellitus (T2DM). Subjects were diagnosed as diabetes mellitus, and admitted to the hospital. The purpose was to evaluate diabetic status in detail, to provide two types of diabetic meal which are calorie restriction (CR) and low carbohydrate diet (LCD), and to make them to understand the importance of nutritional therapy for diabetics.

Regarding the methods, we have continued our diabetic formula protocol of treatment and research program. We proceeded a certain criteria in the following:

- The subjects in this study were diagnosed as T2DM. Other types of diabetes such as type 1 diabetes mellitus (T1DM) or specific rare type of diabetics were excluded. The subjects were not given medicine which may influence glucose metabolism or glucose variability.
- Diabetic patients were admitted for 2 weeks for exam and treatment in the hospital. On the next morning of the admission day, which is day 2 morning, we ordered basal blood test after overnight fast. They included several basal biomarkers such as complete blood count, liver, renal lipids and so on. As to specific exam items for diabetes, blood values of HbA1c, glucose, IRI, C-peptide, HOMA-R, HOMA- β , M value were obtained for the study.
- Our protocol test has nutritional therapy in the following. Subjects have on CR meal on day 1 and day 2, in which CR contains PFC ratio is 15: 25: 60 with 1400 kcal/day. This standard meal is from the proposal of Japan Diabetes Association (JDA) [20].
- Patients were given LCD meal from day 3 to 14 with super LCD. The content has 12% of carbohydrate with 1400 kcal/day. This is called super LCD, and this has been popular and used for LCD promotion activity in Japan. We have other two formula, which are standard LCD with carbohydrate 26% and petite LCD with carbohydrate 40%. These 3 types of LCD have been educated and known to people so far. In current study, all subjects took only super LCD with 12% of carbohydrate.
- Biomarkers related to diabetes were measured in day 2, day 4 and day 14. Blood samples in both days were drawn in the morning after overnight fasting. Both data and several correlations were compared and investigated. The reason of exam on day 2 and day 4 is the comparison of glucose variability after 2 days of LCD meal. On contrast, the reason of exam on day 2 and day 14 is the comparison with lipid metabolism after 12 days of LCD meal.

3.1 Glucose variability a day

For the study of glucose variability, we measured the daily profile of blood glucose on day 2 and day 4. In each day, blood glucose values were checked 7 times a day, which were 08, 10, 12, 14, 17, 19 and 22h. After measuring the glucose data, average blood glucose per day and also the level of M value were calculated using the formula equation [21,22].

3.2 M value

M value has been one of the useful biomarker for glucose variability. It means two crucial aspects for glucose variability. One is the level of the average blood glucose in a day, and another is the degree of swinging glucose in a day, which is called as the mean amplitude of glycemic excursions (MAGE) [21-23].

Consequently, M value is expressed as a numerical value including the meaning for two important markers. They are the degree of elevated blood glucose and increased fluctuation of blood glucose. According to the mathematical equation, M value can be easily calculated as the method of logarithmic transformation. It can be said that the significance of M value expresses the glucose deviation from the ideal glucose variability [22-24].

The method of calculation of M value has three steps. At first, the important equation is that $M = M^{BS} + M^W$: M value expresses the total of M^{BS} and M^W . In the next step, M^W expresses (maximum blood glucose – minimum glucose)/20. In third step, M^{BS} is the mean of MBSBS. When these are summarized, MBSBS has been the individual M-value for each blood glucose, calculated as (absolute value of $[10 \times \log(\text{blood glucose level}/120)]^3$) [22-24].

Concerning the level of M value, clinical judgement for glucose variability can be used for general. There is standard normal range of M value as follows: less than 180 is normal, from 180 to 320 would be borderline, more than 320 would be abnormal.

3.3 Statistical analysis

Concerning this study, data were expressed by the mean and standard deviation. Furthermore, several data were also expressed as the median and the quartile of 25% and 75%. In the case of the comparison among some groups, we used the method of boxplot. It can express 5 data simultaneously, which are the median and the quartile of 25% / 75 % from the box, maximum and minimum from the upper and lower lines. Regarding the correlation with biomarkers, we used the Spearman test for the correlation coefficients. Moreover, the computerized standard statistical tool has been used for analytical evaluation [25].

3.4 Ethical Considerations

Current investigation was basically conducted in compliance with the ethical principles based upon the Declaration of Helsinki. Furthermore, additional commentary was performed in the Ethical Guidelines for Medical Research in Humans and in accordance with the Good Clinical Practice (GCP), which were with the ongoing consideration to the protection of subjects' human rights. In addition, adequate guideline was used, which was the "Ethical Guidelines for Epidemiology Research" by the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labor and Welfare. The author and colleague researchers have had an ethical committee. In the case of discussion, medical doctor, nurse, pharmacist, nutritionist and other experts in the legal specialty attended. Concerning this study, we have discussed and confirmed that this study would be valid and agreed. In addition, the informed consents and written paper agreements have been obtained from the subjects. This study has been registered by National University Hospital Council of Japan (ID: #R000031211).

4. Results

4.1 Basal data

In this study, 81 female patients with T2DM were enrolled and their basal data were summarized in TABLE 1. Average age was 62.4 years old with 64 years old in median. Median value of HbA1c, fasting blood glucose and IRI was 7.2%, 147 mg/dL and 6.8 μ U/mL, respectively. Median value of HOMA-R and HOMA- β was 2.5 and 28.7, respectively.

TABLE 1. Subjects and basal data.

		Mean \pm SD	Median [25%-75%]
Subjects	age (years old)	62.4 \pm 11.8	64[55-70]
	number (M/F)	81 (0/81)	81(0/81)
	No. in group (1, 2, 3, 4)	20, 20, 20, 21	20, 20, 20, 21
Glucose profile	HbA1c (%)	7.8 \pm 1.8	7.2[6.4-8.5]
	Fasting Glucose (mg/dL)	155 \pm 46.2	147[120-180]
	Fasting IRI (μ U/mL)	8.0 \pm 5.1	6.8[4.3-10.3]
HOMA calculation	HOMA-R	2.9 \pm 1.9	2.5[1.5-3.9]
	HOMA- β	37.9 \pm 34.3	28.7[16.6-48.0]

4.2 Biomarkers in day 2 vs day 4

In response to the LCD meal, the values of biomarkers between day 2 and day 4 were compared in TABLE 2. Decreased median values from day 2 vs day 4 were observed in average blood glucose, M value and urinary C-peptide immunoreactivity (CPR), which were 173 vs 130 mg/dL, 62.4 vs 9.6, 54.0 vs 44.0 mg/dL, respectively.

TABLE 2. Comparison of the data on day 2 and day 4.

		Mean \pm SD	median [25% - 75%]
Average glucose	Day 2 (mg/dL)	187 \pm 65.1	173[135-221]
	Day 4 (mg/dL)	140 \pm 40.5	130[108-159]
M value	Day 2	146 \pm 198	62.4[17.8-179]
	Day 4	30.6 \pm 51.0	9.6[4.9-24.6]
Urine C-Peptide	Day 2 (mg/day)	66.3 \pm 37.9	54.0[41.0-78.6]
	Day 4 (mg/day)	52.3 \pm 29.3	44.0[33.4-62.1]

4.3 Lipid profile on day 2 vs day 14

Lipid profile was studied between day 2 and day 14 in response to LCD for 12 days. Both blood sampling were performed after overnight fasting without influence of meal (TABLE 3). The median values of day 2 vs day 14 were measured in triglyceride, HDL-C and LDL-C, which were 103 vs 79 mg/dL, 62 vs 56 mg/dL, and 131 vs 139 mg/dL, respectively.

TABLE 3. Lipid metabolism between day 2 and day 14.

		Mean ± SD	Median [25% - 5%]
Triglyceride (mg/dL)	Day 2 (mg/dL)	120 ± 61.3	103[78.0-151]
	Day 14 (mg/dL)	82.8 ± 29.6	79.0[60.3-94.8]
HDL-C (mg/dL)	Day 2 (mg/dL)	63.8 ± 15.2	62.0[52.8-69.5]
	Day 14 (mg/dL)	58.6 ± 14.6	56.0[48.0-65.3]
LDL-C (mg/dL)	Day 2 (mg/dL)	134 ± 39.6	131[107-158]
	Day 14 (mg/dL)	147 ± 41.4	139[122-171]

4.4 Biomarkers on day 2

The values of HbA1c and average glucose on day 2 in each group were shown in FIG. 1. The median data in 4 groups were 6.0, 7.0, 7.9, 9.4% and 123, 155, 193, 264 mg/dL, respectively.

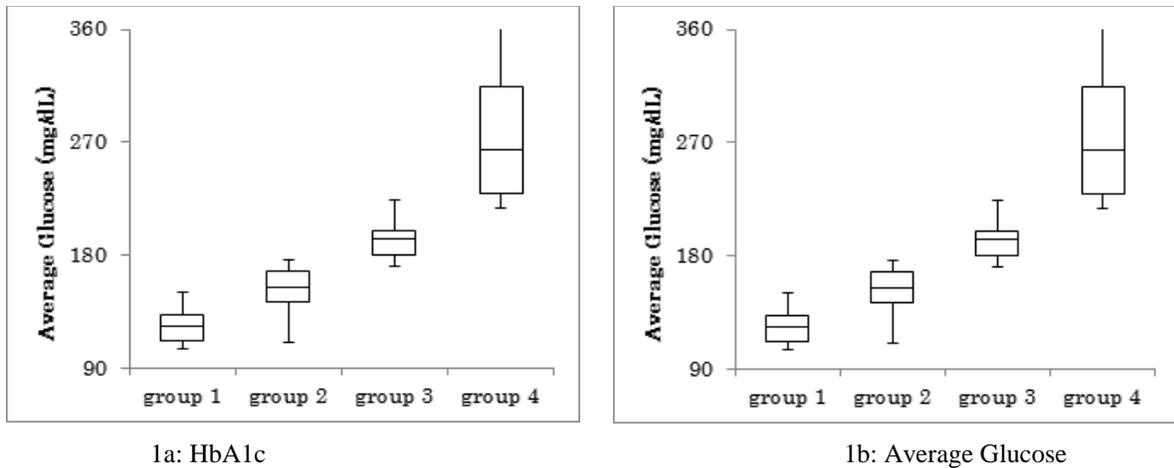


FIG. 1. HbA1c and average glucose on day 2 in each group.

Similarly, the data of HOMA-R and HOMA-β were 2.1, 2.5, 2.2, 2.6 and 48.5, 39.1, 21.3, 16.3, respectively (FIG. 2). The former did not show the difference in 4 groups, but the latter showed the decreasing data from group 1 to 4.

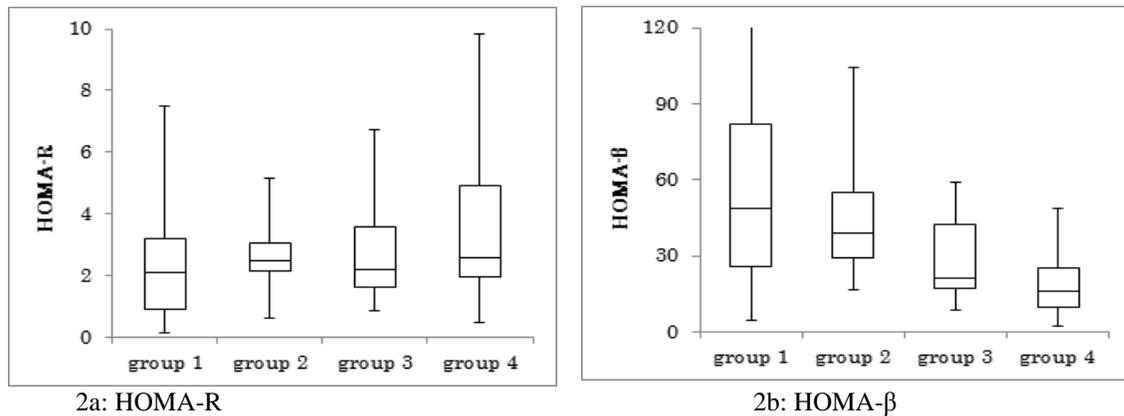
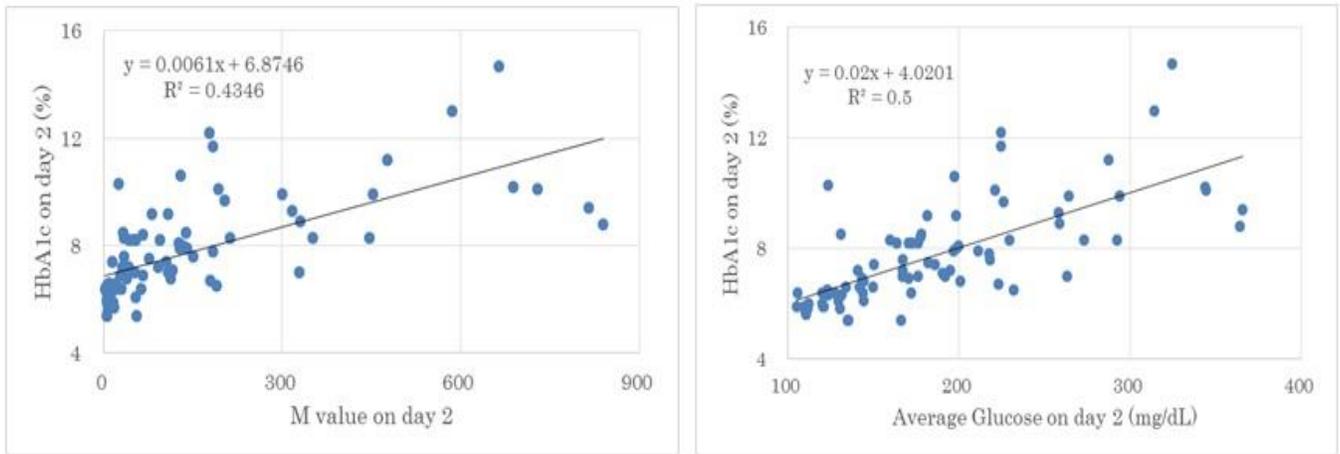


FIG. 2. HOMA-R and HOMA-β on day 2 in each group.

The correlations of the data in day 2 among biomarkers were investigated. There was significant correlations between M value and HbA1c ($p < 0.01$), and between average glucose and HbA1c ($p < 0.01$) (FIG. 3).



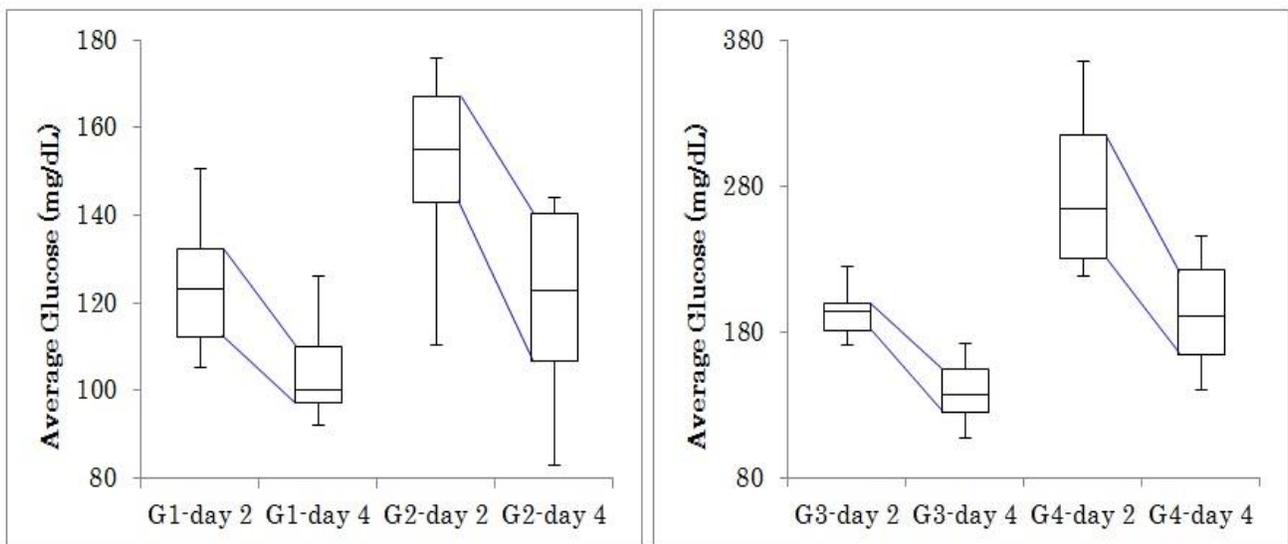
3a: M value and HbA1c

3b: Average Glucose and HbA1c

FIG. 3. Correlation among HbA1c, average glucose and M value on day 2.

4.5 Comparison on day 2 vs day 4

The values of average glucose on day 2 vs day 4 were compared in 4 groups (FIG. 4). The median value in each group was 122 vs 99 mg/dL, 155 vs 123 mg/dL, 193 vs 136 mg/dL, 264 vs 190 mg/dL, respectively. There were remarkable decrease during 2 days in all groups.



4a: group 1 and 2

4b: Group 3 and 4

FIG. 4. Changes in average glucose from day 2 to 4 in each group.

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 7.5 vs 8.2, 37.2 vs 6.2, 111 vs 9.7, 330 vs 67, respectively. In group 1, the data of M value was not changed. In group 2,3,4, there were remarkable decrease of M value during 2 days.

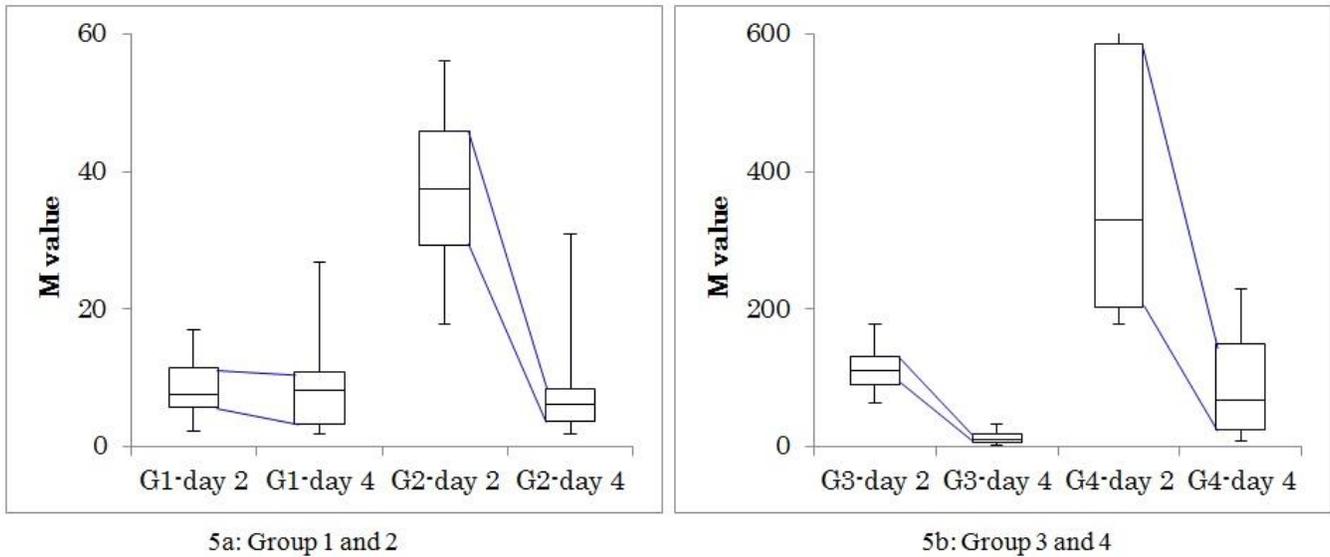


FIG. 5. Changes in M value from day 2 to 4 in each group.

4.6 Correlation between on day 2 and day 4

The values of average glucose and M value were compared between on day 2 and day 4 (FIG.6). There were significant correlations in both, with remarkable high correlation coefficient.

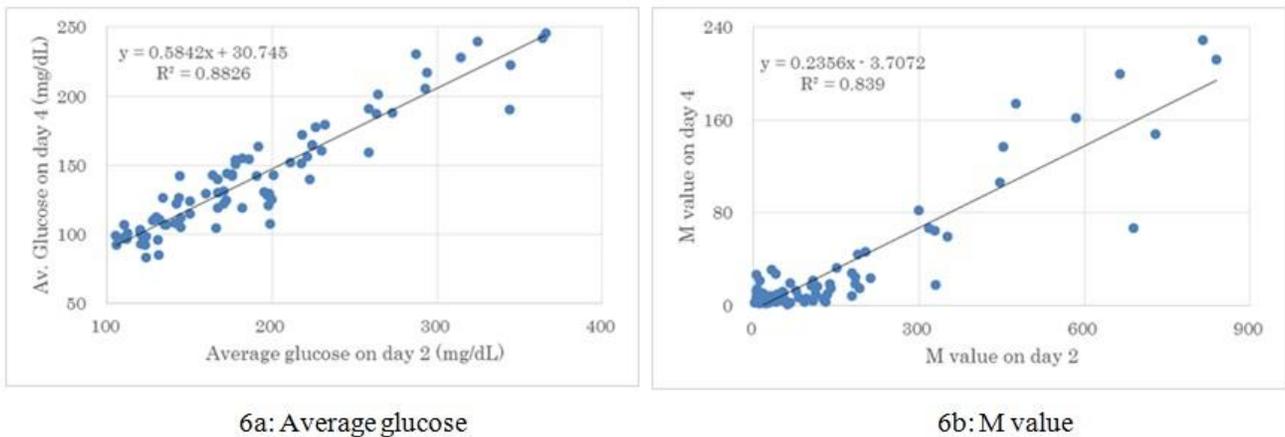


FIG. 6. Correlations of glucose and M value between day 2 and 4.

4.7 Lipid profile on day 2 and day 14

The levels of triglyceride on day 2 vs day 14 were compared in 4 groups (FIG.7). The median value in each group was 116 vs 74 mg/dL, 109 vs 82 mg/dL, 89 vs 75 mg/dL, 89 vs 79 mg/dL, respectively. There were decrease in all groups.

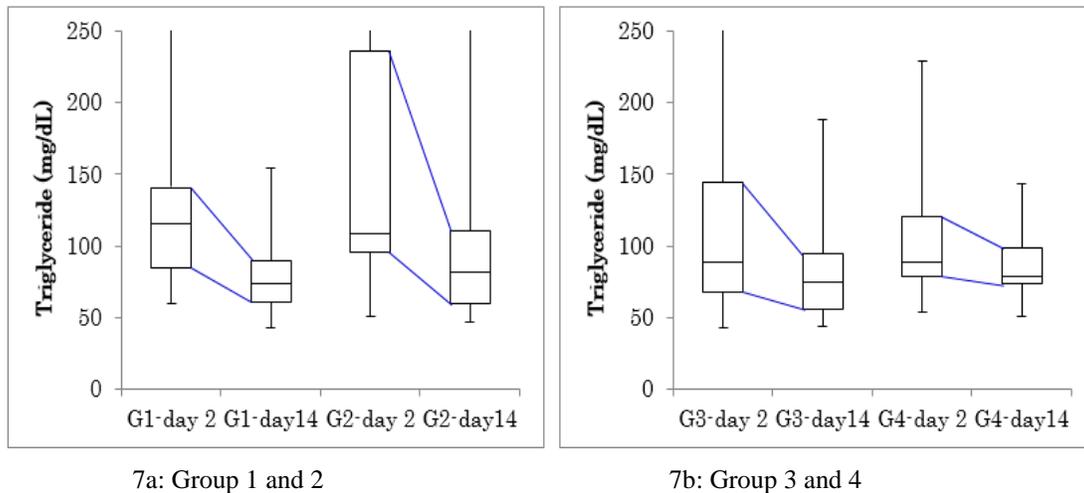


FIG. 7. Changes in Triglyceride from day 2 to 14 in each group.

5. Discussion

In our medical practice, we have provided treatment on many cases of metabolic syndrome, obesity and diabetic patients. At the same time, we have continued clinical research, and spread the information and tips of how to continue LCD with three types of LCD meals. Simple and recommended methods are super LCD, standard LCD and petite LCD with the carbohydrate 12%, 26% and 40%, respectively [18,19]. As a result, medical and social understanding for LCD has been found in recent years [14,26].

In this study, we studied the detail investigation for glycemic variability on 81 female patients with T2DM. In the research design, limitation of female was due to the fact that diabetic research usually has heterogeneous factors, then trying to have common factors in the background. In addition, they were categorized into 4 groups according to the level of M value. It is an index of hyperglycemia and blood sugar fluctuation range, which seemed to be useful for the analysis for the data. The results of this study are shown in Tables and Figures, and are discussed in this order.

The background of the subject and obtained data were shown in two ways. In addition to the conventional description, average \pm standard deviation (SD), the median and quartile 25% and 75% are also calculated and shown by box plot (box-and-whisker plot) method [27]. Although it is rather difficult to grasp the whole situation with the former data only, the latter method can show the general condition. The reason is that the box range represents the width of 50% of the subjects in the group. In particular, since the fluctuation range of the M value is large, it is reasonable to judge by the median value rather than the average value.

Three biomarkers which are mean glucose, M value and urinary CPR decreased remarkably by LCD diet only for 2 days, suggesting the clinical effect in short period [28]. Among the, M value markedly decreased in particular. Indicating both mean blood sugar and fluctuation range, M value seems to be useful for grasping blood glucose fluctuation [16]. Furthermore, in the case of follow-up study and observations, variations in M value can indicate more significant than

fluctuations in blood glucose [29,30]. Consequently, the detail differences can be captured by M value, associated with the usefulness for clinical research in the future.

We divided into 4 groups according to the level of M value. As to HbA1c and mean blood glucose, they showed less overlap area and rather well-divided distribution, suggesting that the grouping would be appropriate and useful. In the distribution of 4 groups, the overlap was broad in HOMA-R and the distribution was rather divided in HOMA- β . The former shows insulin resistance and the latter shows the insulin secretion ability from β cells of the pancreas [31]. From the above, it seems that relationship with insulin secretion would be related to the higher blood glucose and wider fluctuation of glucose.

Significant correlation was found among the biomarkers of HbA1c, mean blood glucose and M value. The correlation coefficients were roughly the same as $r^2 = 0.43$ and $r^2 = 0.5$. The correlation coefficient between the average blood glucose and the M value is very high, since the M value is calculated from the average blood sugar value [22,23]. HbA1c expresses the average glucose variability over the past month, while mean blood glucose directly represents the blood glucose fluctuation of the day studied [24,25]. Various clinical studies of diabetes seem to be possible by utilizing these three biomarkers.

In the study of 4 groups, the average blood glucose and M value generally dropped between day 2 and day 4. Among them, the M value was almost the same in group 1 of the M value. The reason is based on the calculation formula of M value [22-25]. Since the standard level of blood glucose is 120 mg / dL, the M value is the smallest when the glucose is around 120 mg/dL [32,33]. If the average glucose changes from 120 mg/dL to 100 mg/dL, M value changes from the minimum to higher value.

It was observed that M value of group 2 and 3 decreased to less than 10 on day 4. This is from the fact that means blood glucose was decreased to 123mg/dL and 136 mg/dL, respectively. When observing the boxplot of mean blood glucose and M value in group 4, it is clearly understood that the change in blood glucose was improved in 50% of the subjects indicated by the box area.

From day 2 to day 4, average blood glucose and M value decreased in the same way. Observing the correlation coefficient, it is very high with $R^2 = 0.88, 0.84$, respectively. In other words, it can be said that the reduction rate of corresponding data is about the same level as a whole [14,34]. The regression curve of blood glucose is $y = 0.58x + 30.7$, indicating the sufficient effect of LCD only for 2 days [14,35]. When we enter $x = 200$ into the equation, the calculation shows that $y = 147$. As to M value, the regression curve is $y = 0.24x - 3.7$. Since the slope is small which is 0.24, the M value becomes much lower in comparison with the data of day 2 and day 4.

For the lipid profile, the value of TG was sufficiently reduced for 12 days of LCD. Our results were consistent with previous reports [13,26]. On the other hand, the trend of HDL-C rise and LDL-C declining tendency was not clear. According to the previous report [13], TG will decline in a short period of time by LCD, and after several months HDL-C will show a slight upward trend. On contrast, LDL-C has been not variable, which are rising, constant or decreasing [26]. Although it was a short period in this study, TG descends sufficiently, indicating clinical effect of LCD. As mentioned above, we described

various speculations from the results of. However, there is limit in this research. Although the effects of the LCD were observed under the current conditions, the effect will be different in the actual life of each patient. Then, further evaluation under various situations would be necessary. Furthermore, three types of LCDs proposed by us would be useful for various diabetic patients, which are super, standard, petite LCD meal in their daily lives.

5. Conclusion

In summary, we investigated 81 female patients with T2DM. Diabetes related biomarkers including HbA1c, glucose, IRI, HOMA-R, HOMA- β were measured and correlations were investigated. In response to LCD for only 2 days, average glucose level, M value and urinary C-peptide excretion were remarkably decreased. Triglyceride value was decreased for LCD in 12 days. These results suggest that LCD would be clinically effective for T2DM and these findings would become reference and basal data in this research, leading to future research development.

6. Acknowledgement

As to this study, some part of the content was presented at annual congress of Japan Diabetes Society (JDS) Congress, Tokyo, 2018. The authors would like to express gratitude all staffs and patients for the understanding and cooperation.

7. Conflicts Of Interest

The authors state that there are no conflicts of interest as regard to this report.

REFERENCES

1. World Health Organization Global report on diabetes. WHO, Geneva, Switzerland; 2016.
2. Defronzo RA. Banting Lecture from the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes*. 2009;58(4):773-95.
3. Ojo O. An overview of diabetes and its complications. *Diabetes Res Open J*. 2016;2(2):e4-e6.
4. Dunning T. *Care of People with Diabetes: A Manual of Nursing Practice*. New Jersey: Wiley Blackwell, USA; 2014.
5. Williams G, Pickup JC. *Handbook of Diabetes*. 3rd ed. New Jersey: Blackwell Publishing, USA; 2004.
6. International Diabetes Federation (IDF) Standards of Medical Care in Diabetes-2015. *Diabetes Care*. 2015;38:S1-S94.
7. <http://www.acponline.org/clinical-information/guidelines>.
8. American Diabetes Association Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2018. *Diabetes Care*. 2018;41(1):S73-S85.
9. Bando H. Statement for Diabetes Guideline Has Been on Discussion for Future Better Lives. *J Endocrinol Thyroid Res*. 2018;3(4):555616.
10. Bernstein RK. *Dr. Bernstein's Diabetes Solution*. Little, New York: Brown and company; 1997.
11. Shai I, Schwarzfuchs D, Henkin Y, et al. Weight Loss with a Low-Carbohydrate, Mediterranean, or Low-Fat Diet. *N Engl J Med*. 2008;359(3):229-41.
12. Schwarzfuchs D, Golan R, Shai I. Four-year follow-up after two-year dietary interventions. *N Engl J Med*. 2012;367: 1373-4.

13. Accurso A, Bernstein RK, Dahlqvist A, et al. Dietary carbohydrate restriction in type 2 diabetes mellitus and metabolic syndrome: time for a critical appraisal. *Nutr Metab (Lond)*. 2008;5:9.
14. Meng Y, Bai H, Wang S, et al. Efficacy of low carbohydrate diet for type 2 diabetes mellitus management: A systematic review and meta-analysis of randomized controlled trials. *Diabetes Res Clin Pract*. 2017;131:124-31.
15. Ebe K, Ebe Y, Yokota S, et al. Low Carbohydrate diet (LCD) treated for three cases as diabetic diet therapy. *Kyoto Med Association J*. 2004;51:125-29.
16. Bando H, Ebe K, Muneta T, et al. Effect of low carbohydrate diet on type 2 diabetic patients and usefulness of M-value. *Diabetes Res Open J*. 2017;3(1):9-16.
17. Muneta T, Kawaguchi E, Nagai Y, et al. Ketone body elevation in placenta, umbilical cord, newborn and mother in normal delivery. *Glycative Stress Research*. 2016;3(3):133-40.
18. Ebe K, Bando H, Yamamoto K, et al. Daily carbohydrate intake correlates with HbA1c in low carbohydrate diet (LCD). *J Diabetol*. 2018;1(1):4-9.
19. Bando H, Ebe K, Muneta T, et al. Clinical Effect of Low Carbohydrate Diet (LCD): Case Report. *Diabetes Case Rep*. 2017;2(2):124.
20. Japan Diabetes Association. *Diabetes clinical practice guidelines Based on scientific evidence*. 2013.
21. Schlichtkrull J, Munck O, Jersild M. The M-value, an index of blood sugar control in diabetics. *Acta Med Scand*. 1965;177(1):95-102.
22. Service FJ, Molnar GD, Rosevear JW, et al. Mean amplitude of glycemic excursions, a measure of diabetic instability. *Diabetes*. 1970;19(9):644-55.
23. Molnar GD, Taylor WF, Ho MM. Day-to-day variation of continuously monitored glycaemia: A further measure of diabetic instability. *Diabetologia*. 1972;8(5):342-8.
24. Moberg E, Kollind M, Lins PE, et al. Estimation of blood-glucose variability in patients with insulin-dependent diabetes mellitus. *Scand J Clin Lab Invest*. 1993;53(5):507-14.
25. Yanai H. *Four step excel statistics*, 4th ed. Tokyo: Seiun-sha Publishing Co.Ltd, Japan; 2015.
26. Feinman RD, Pogozelski WK, Astrup A, et al. Dietary carbohydrate restriction as the first approach in diabetes management: Critical review and evidence base. *Nutrition*. 2015;31(1):1-13.
27. Williamson DF, Parker RA, Kendrick JS. The box plot: a simple visual method to interpret data. *Ann Intern Med*. 1989;110(11):916-21.
28. Williamson DF. The Box Plot: A Simple Visual Method to Interpret Data. *Ann Intern Med*. 1989;110(11):916.
29. Bando H, Ebe K, Muneta T, et al. Urinary C-Peptide Excretion for Diabetic Treatment in Low Carbohydrate Diet (LCD). *J Obes Diab*. 2018;1(1):13-8.
30. Borg R, Kuenen JC, Carstensen B, et al. The ADAG Study Group (2011) HbA_{1c} and mean blood glucose show stronger associations with cardiovascular disease risk factors than do postprandial glycaemia or glucose variability in persons with diabetes: the A1C-Derived Average Glucose (ADAG) study. *Diabetologia*. 2011;54(1):69-72.
31. Kilpatrick ES, Rigby AS, Atkin SL. Effect of Glucose Variability on the Long-Term Risk of Microvascular Complications in Type 1 Diabetes. *Diabetes Care*. 2009;32(10):1901-3.
32. Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985;28(7):412-9.
33. DeVries JH. Glucose Variability: Where It Is Important and How to Measure It. *Diabetes*. 2013;62(5):1405-8.

34. Fritzsche G, Kohnert KD, Heinke P, et al. The Use of a Computer Program to Calculate the Mean Amplitude of Glycemic Excursions. *Diabetes Technol Therap.* 2011;13(3):319-25.
35. Hill NR, Oliver NX, Choudhary P, et al. Normal Reference Range for Mean Tissue Glucose and Glycemic Variability Derived from Continuous Glucose Monitoring for Subjects Without Diabetes in Different Ethnic Groups. *Diabetes Technol Ther.* 13(9):921-8.