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Research Article

Short Term Effect of Low Carbohydrate Diet in Diabetic Male Patients

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Abstract

Background: Low Carbohydrate Diet (LCD) and Calorie Restriction (CR) have been discussed for long. Authors have continued clinical research on LCD, CR and M value.

Subjects and Methods: Subjects were 67 male patients with type 2 diabetes mellitus (T2DM). Methods were i) daily profile of blood glucose, average glucose, M value for CR meal, ii) same exam of i) after 2 days of LCD, iii) Delta and AUC ratio for 70g of carbohydrate (0 - 30 minutes) in meal tolerance test (MTT), iv) Triglyceride check for 12 days of LCD, v) analyses of correlation of biomarkers.

Results: Obtained data were as follows: average age 61.2 years old, median values are HbA1c 7.8%, fasting glucose 151 mg/dL, IRI 4.4 μU/mL, HOMA-R 2.1, HOMA-β 15.9, respectively. Median values on day 2 vs 14: average glucose 198 vs 151 mg/dL, M value 134 vs 14.4, respectively. AUC ratio for Carbo70 showed more separate distribution as insulin secretion ability than Delta ratio. There were significant correlations among HbA1c, average glucose and M value.

Discussion and Conclusion: These results suggested that LCD would have beneficial effects for glucose variability. Furthermore, it would become basal and reference data for the future research development in this field.

Keywords: *Low Carbohydrate Diet (LCD); Blood Glucose Profile; Morbus Value (M Value); Delta Ratio of Carbo70; Meal Tolerance Test (MTT)*

Abbreviation

LCD: Low Carbohydrate Diet; T2DM: Type 2 Diabetes Mellitus; IRI: Immunoreactive Insulin; HOMA-R: Homeostasis Model Assessment of Insulin Resistance; HOMA-β: Homeostasis Model Assessment of β Cell Function

Introduction

There have been serious situation concerning diabetes across the globe. Diabetic prevalence, deaths attributable to diabetes, and health expenditure has increased with social, financial and health system implications [1]. Age-standardized diabetes prevalence in adults since 1980 in the world has increased or at best remained unchanged [2]. The problem of diabetes in terms of prevalence and number of adults has increased faster in low- and middle-income countries than in high-income countries [2]. New data showed the estimation in United States, where diagnosed type 2 diabetes was 8.6%, representing 21.0 million US adults [3].

In order to prevent and treat diabetes, medical diabetic societies in some countries have presented their guidelines for years. Recently, some changes in the guideline concerning the goal of the treatment for diabetes. European Diabetes Society (EASD) 2012 proposed the joint algorithm [4]. Consequently, American Diabetes Association (ADA) presented the official comment in 2017 [5]. There was an impressive proposal about the standard value concerning the goal of HbA1c value [6]. The crucial point was that management goal for HbA1c in most type 2 diabetic patients would be 7% or more and less than 8%. This impact was so large to influence much for several diabetic societies. Against the proposal for ACP, ADA announced an objection at once [7]. Consequently, diabetic management has been in discussion with some diabetic guidelines.

For the treatment for diabetes and metabolic syndrome (Met-S), nutrition therapy has to be essential. Calorie restriction (CR) diet has been the ordinary nutritional treatment method for years. However, Atkins and Bernstein initiated Low Carbohydrate Diet (LCD) in 1980-90' in western countries [8,9]. LCD has been gradually popular, and the effect of LCD for weight reduction and glucose lowering has been reported. Consequently, LCD showed rather predominant efficacy compared with Mediterranean and low fat diet in the Dietary Intervention Randomized Controlled Trial (DIRECT) study [10,11]. Discussion on CR and LCD has been observed until now, with clinical various predominant effects of LCD [12,13].

On contrast in Japan, authors and colleagues have introduced LCD in Japan [14]. After that, we have continued and developed LCD movement using the recommendation of simple way of LCD in 3 types, which are super LCD, standard LCD and petite LCD meals [15,16].

Furthermore, we reported the proposal of application of the breakfast of CR meal. In similar method of insulinogenic index (IGI) for 75g oral glucose tolerance test (OGTT), 70g of carbohydrate in CR can be enough applied for insulin/glucose responses in meal tolerance test (MTT) [17].

By applying these researches mentioned above, we have investigated the pathophysiology of glucose variability in patients with type 2 diabetes mellitus (T2DM). In this study, we provide CR and LCD and compared several biomarkers.

Subjects and Methods

Subjects were 67 patients with T2DM. They were recently diagnosed as diabetes mellitus and admitted to the hospital. The purpose of admission was to evaluate diabetic condition in detail, to give two types of diabetic formula including CR and LCD, and to make them to have and remember the experience of nutritional therapy for diabetics.

As to the fundamental methods, we have our diabetic research formula program of further evaluation and treatment. We have performed a certain criteria as follows:

1. Subjects enrolled were previously diagnosed as T2DM. We excluded other types of diabetes such as type 1 diabetes mellitus (T1DM) or specific rare type of diabetics. Patients with T2DM have not given diabetic medicine possibly influencing glucose variability. We used the criteria about the immunoreactivity insulin (IRI) value of the subjects in the morning after overnight fast. The subjects with IRI less than 15 μU/mL were included, while the subjects with IRI 15 μU/mL and more than 15 μU/mL were excluded.
2. Subjects were in-patients for 2 weeks for detail evaluation and treatment in the hospital. On the next morning of the admission day, fundamental blood and other tests were performed after overnight fast. The general blood tests were done including complete blood count, liver, renal lipids and etc. Regarding diabetic specific exams, blood values of HbA1c, glucose, IRI, C-peptide, HOMA-R, HOMA-β, M value were measured and calculated for the study.
3. The detail contents of nutritional therapy were in the following: In-patients eat CR meal on day 1 and 2, which has P: F: C ratio = 15: 25: 60 with 1400 kcal/day. This meal is along the standard formula from Japan Diabetes Association (JDA) [18].
4. Subjects enrolled were provided LCD meal from day 3 to 14 with super LCD, including 12% of carbohydrate with 1400 kcal/day. This is called super LCD that has been prevalent and used for our activity of LCD promotion in Japan. We have used the application of other two formula, which are standard LCD with carbohydrate 26% and petite LCD with carbohydrate 40%. These 3 types of formula for LCD have been educated for lots of people until now.
5. Several biomarkers related to diabetes were measured in day 2, 4 and 14. Those blood samples were drawn in the morning after overnight fast. Both data and several correlation 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.

Study protocol

Methods included 3 patterns of research in this study. The protocol of these studies is described in the following, respectively.

Study 1: On the morning of day 2, breakfast with 70g of carbohydrate was provided to the subjects. The values of glucose and IRI on 0 minute and 30 minutes were measured. By these data, response of increment of IRI/increment of glucose was calculated, which is similar to insulinogenic index (IRI) for 75g OGTT. We adapted two ways of method for the response of insulin / glucose (IRI/Glu) ratio. One is delta ratio of IRI/Glu using the increment value, and another is AUC ratio of IRI/Glu using the Area Under the Curves (AUC) for the calculation.

Study 2: Daily profile of glucose was investigated on day 2 (CR) and day 4 (LCD). Blood samples were drawn 7 times as the clock time 08, 10, 12, 14, 17, 19, 22h. From the previous papers, there observed the similar and compatible results in comparison with 7-times sampling and 20 times sampling [19,20]. It has also the compatible results compared with the data from the continuous glucose monitoring (CGM) [19,20]. 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]. M value means the total of the elevated glucose level and also the increased mean amplitude of glycemic excursions (MAGE).

Study 3: Lipid value was investigated on day 2(CR) and day 14 (LCD). Blood samples were drawn in the morning after overnight fast. Values of triglyceride, HDL-C, LDL-C were measured and compared.

Study 4: According to the average glucose value, Subjects were categorized into 5 groups. Values of several biomarkers were compared among the groups.

Responses of glucose and insulin

In order to evaluate the insulin secretion ability, MTT was performed including 70g of carbohydrate. The responses of incremental IRI/glucose has been IGI. Its formula has been the delta (increment) of IRI (0-30 min)/delta (increment) of blood glucose (0 - 30 minutes). In this paper, we applied the same IGI for carbohydrate 70g. It is called the Delta Ratio of IGI for Carbo70.

Another calculation method was applied. For the usage of square of the AUC, the responses of glucose and insulin were described. In comparison with the square area size, the ratio of IRI/glucose ratio was measured. It is called the AUC Ratio of IGI for Carbo70.

In summary of two methods, two formulas are in the following. Delta Ratio of IGI for Carbo70 is (IRI at 30 min - IRI at 0min)(μU/mL)/(Glucose at 30min - Glucose at 0min)(mg/dL). Similarly, AUC Ratio of IGI for Carbo70 is (AUC of IRI for 0-30min)(μU/mL x h)/(AUC of glucose for 0-30min)(mg/dL x h).

M value

M value has been known as the useful biomarker for glucose variability. It has two meaning for two crucial aspects for glucose variability. One is the elevated average of blood glucose in a day, and another is the increased degree of swinging glucose in a day, the mean amplitude of glycemic excursions (MAGE) [19-21].

Thus, M value has been expressed as a numerical value including two clinical significance. Due to the mathematical equation, M value can be easily calculated as the formula of logarithmic transformation. Consequently, the significance of M value has been said to express the glucose deviation from the ideal glucose variability [20-22].

The calculation method of M value has three steps. Firstly, the important equation is the basis of the formula that $M = M^{BS} + M^{W}$: M value expresses the total of M^{BS} and M^{W}. Secondly, M^{W} expresses (maximum blood glucose − minimum glucose)/20. Thirdly, M^{BS} is the mean of MBSBS. Summarized the method above, MBSBS has been the individual M-value for each blood glucose, calculated as (absolute value of [10 × log (blood glucose level/120)])^3 [20-22].

For the data of M value, clinical evaluation for glucose variability can be used for general. There is standard normal range of M value as follows: < 180 is normal range, from 180 to 320 would be around borderline, more than 320 would be abnormal range.

Statistical analysis

Regarding current investigation, data were expressed by the mean and standard deviation. In addition, several data were also described as the values of median and quartile of 25% and 75%. Compared the data among some groups, the method of boxplot was

utilized. It can express 5 data simultaneously, which means the median and the quartile of 25%/75% from the box drawing, maximum and minimum from the upper and lower straight lines. As to the correlations among several biomarkers, we used the Spearman test for the correlation coefficients. Furthermore, we used the computerized standard statistical tool for analytical evaluation [23].

Ethical considerations

This study was fundamentally conducted in compliance with the ethical principles based upon the Declaration of Helsinki. Moreover, additional commentary was performed in the Ethical Guidelines for Medical Research in Humans and in accordance with the Good Clinical Practice (GCP). They were with the ongoing consideration to the protection of subjects' human rights. Furthermore, adequate guideline was used, including the "Ethical Guidelines for Epidemiology Research" by the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labor and Welfare, Japan.

Author and colleagues have an ethical committee for the study. In the case of discussion, medical doctor, nurse, pharmacist, nutritionist and other experts in the legal specialty attended. As to current investigation, we have discussed and confirmed that this protocol would be valid and agreed. Further, 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).

Results

Basal data

In current study, 67 male patients with T2DM were enrolled and the basal data were summarized in table 1. Average age was 61.2 years old with 63 years old in median. Median value of HbA1c, fasting blood glucose and IRI was 7.8%, 151 mg/dL and 4.4 μU/mL, respectively. Median value of HOMA-R and HOMA-β was 2.1 and 15.9, respectively.

		Mean ± SD	Median [25% -75%]
Subjects	Age (Years old)	61.2 ± 0.1	63 [56 - 68]
	Number (M /F)	67 (67/0)	67 (67/0)
	No. in group 1-5	13,13,13,14,14	13,13,13,14,14
Glucose Profile	HbAlc (%)	7.9 ± 1.8	7.8 [6.5 - 93]
	Fasting Glucose (mg/dL)	169 ± 50.6	151[129 - 212]
	Fasting IR I (μ/mL)	5.4 ±3.5	4.4 [2.6 - 7.4]
HOMA Calculation	HOMA-R	22 ± 1.4	2.1 [1.0 - 2.9]
	HOMA-β	23.8 ± 20.9	15.9 [9.8 - 30.1]

Table 1: *Subjects and basal data.*

Responses of glucose and IRI

Responses of blood glucose and IRI for 70g of carbohydrate were shown in table 2. Similar to IGI to 75gOGTT, Delta ratio and AUC ratio for carbo70 were calculated, in which median data were 0.14 and 4.3.

		Mean ± SD	Median [25% -75%]
Glucose Response	0 min (mg/dL)	169 ± 50.6	151 [129 - 212]
	30 min (mg/dL)	217 ± 55.8	204 [176 - 254]
Insulin Response	0 min (mg/dL)	5.4 ± 3.5	4.4 [2.6 - 7.4]
	30 min (mg/dL)	15.8 ± 13.5	11.6 [7.6 - 19.9]
IRI/BS Response	Delta Ratio	0.24 ± 0.28	0.14 [0.09 - 0.28]
	AUC Ratio	62 ± 5.9	42 [2.7- 7.2]

Table 2: *Reponses of BS and IR I for Carbo70.*

Glucose variability in day 2 vs day 4

Glucose variability in day 2 and day 4 were compared with the standard meal between CR and LCD, respectively (Table 3). The data of average glucose, M value, urinary CPR in day 2 vs 4 were, 198 mg/dL vs 151 mg/dL, 134 vs 14.4, 74.0 mg/day vs 56.4 mg/dL, respectively.

		Mean ± SD	Median [25% - 75%]
Average Glucose	Day 2 (mg/dL)	216 ± 77.1	198 [141-272]
	Day 4 (mg/dL)	157 ±462	151 [121 - 179]
M Value	Day 2	233 ± 273	134 [38.1 - 357]
	Day 4	49.4 ± 95.0	14.4 [4.5 - 45.9]
Urine C-peptide	Day 2 (mg/day)	90.9 ± 48.4	74.0 [57.3 -120]
	Day 4 (mg/day)	76.8 ± 35.1	56.4 [42.1 - 91]

Table 3: *Comparison of the data on day 2 and day 4.*

Lipid profile on day 2 vs day 14

Lipid profile was investigated 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 4). The median values of day 2 vs day 14 were measured in triglyceride, HDL-C and LDL-C, which were 135 vs 82 mg/dL, 57 vs 48 mg/dL, and 117 vs 151 mg/dL, respectively.

		Mean ± SD	Median [25% -75%]
Triglyceride (mg/dL)	Day 2 (mg/dL)	168 ± 131	135 [73 - 202]
	Day 14 (m g/dL)	91.8 ± 44.9	82 [58 - 108]
HDL-C (mg/dL)	Day 2 (mg/dL)	60.5 ± 20.6	57 [45 - 66]
	Day 14 (mg/dL)	55.7 ± 21.4	48 [42 - 67]
LDL-C (mg/dL)	Day 2 (mg/dL)	123 ± 36.4	117 [94.0 -155]
	Day 14 (mg/dL)	141 ± 42.7	151 [109 -176]

Table 4: *Lipid metabolism between day 2 and day 14.*

Comparison among groups

Average blood glucose levels were measured and subjects were classified into 5 groups due to the results. Median average glucose value in each group was 129, 159, 195, 247, and 311 mg/dL, respectively.

The values of HbA1c and M value on day 2 were shown in figure 1. Median data in 5 groups were 6.1%, 6.9%, 7.2%, 8.6%, 9.8% and 13.7, 45.2, 103, 286, 541, respectively.

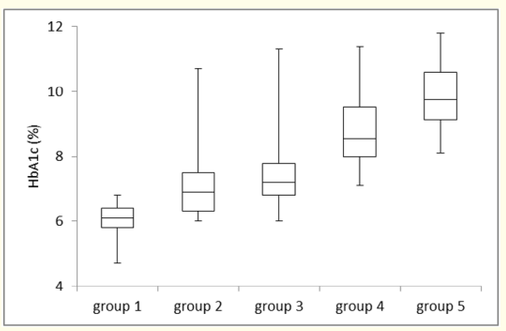

Figure 1a: *HbA1c*

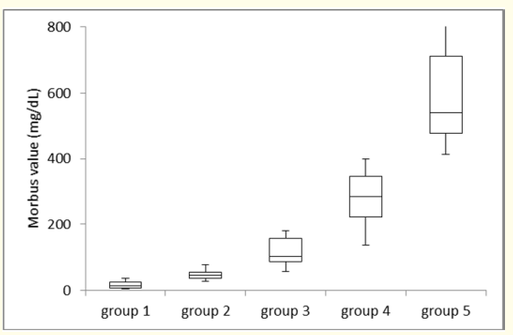

Figure 1b: *M value*

Figure 1: *HbA1c and M value on day 2 in each group.*

The values of HOMA-R and HOMA-β on day 2 were shown in figure 2. Median data in 5 groups were 2.2, 2.1, 2.1, 2.0, 1.8 and 30.9, 28.7, 21.9, 10.7, 5.7, respectively.

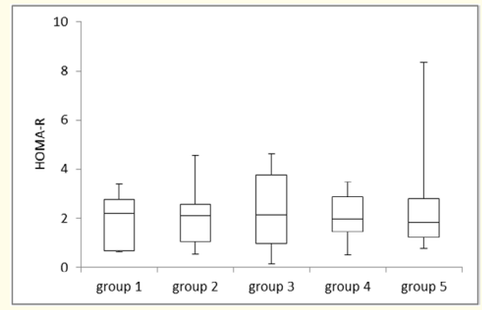

Figure 2a: *HOMA-R*

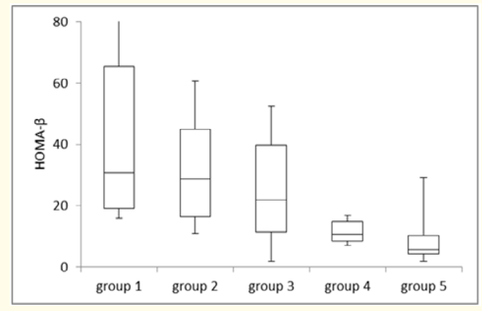

Figure 2b: *HOMA-β*

Figure 2: *HOMA-R and HOMA-β on day 2 in each group.*

The values of IRI/BS response for carbo70 by the method of Delta Ratio and AUC Ratio were shown in figure 3. Median data in 5 groups were 0.3, 0.2, 0.2, 0.1, 0.1 and 9.3, 5.5, 5.0, 3.0, 2.3 respectively.

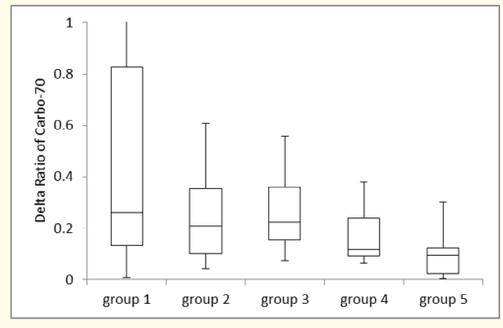

Figure 3a: *Delta Ratio*

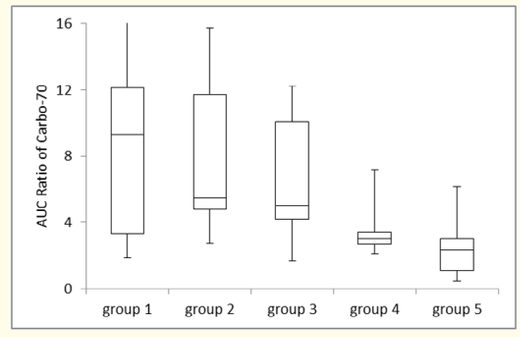

Figure 3b: *AUC Ratio*

Figure 3: *IRI/BS response for carbo70 in each group.*

Correlations among biomarkers

Correlations among HbA1c, average glucose and M value on day 2 are shown in figure 4. There were significant correlations between HbA1c and average glucose, and between HbA1c and M value ($p < 0.01$).

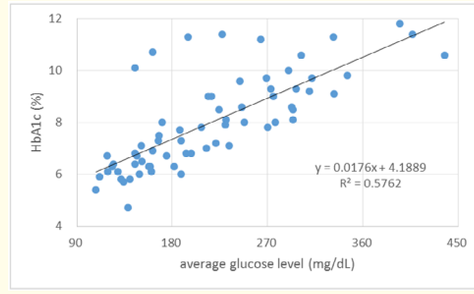

Figure 4a: *Average Glucose and HbA1c*

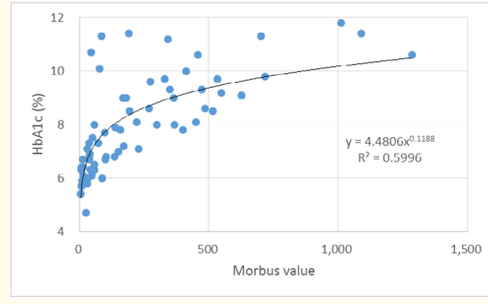

Figure 4b: *M value and HbA1c*

Figure 4: *Correlation among HbA1c, average glucose and M value on day 2.*

Correlations of average glucose and M value between day 2 and 4 were shown in figure 5. There were significant correlations between those between day 2 and 4 ($p < 0.01$).

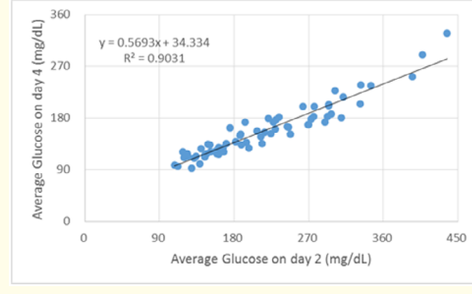

Figure 5a: *Average glucose*

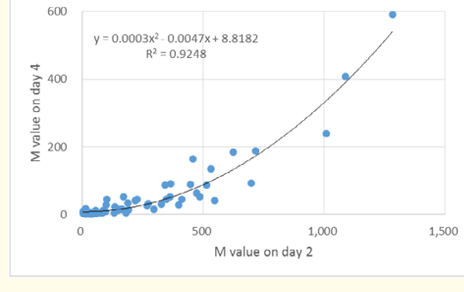

Figure 5b: *M value*

Figure 4: *Correlations of average glucose and M value between day 2 and 4.*

Discussion

Associated with our medical practice with diabetes and metabolic syndrome, we have continued clinical research concerning LCD and CR [14-17]. This research is characterized for several combination of our previous research. They are i) improvement of blood glucose profile for only 2 days trial of LCD [15], ii) clinical application of M value in order to compare the glucose variability between CR and LCD [15,16], iii) clinical trial of MTT instead of 75gOGTT [17], iv) clinical usefulness of MTT for investigation of insulin secretion, v) detail study of HOMA-R and HOMA-β by 5 groups, vi) close correlations among average blood glucose level, M value, HbA1c, and other biomarkers.

In this study, we had obtained various data and described in tables and figures, where our speculation would be discussed in this order. As to the subjects and basal data, there are almost similar data between the mean and median values. One of the reason is the beneficial point of the boxplot method, which is useful in clinical study [24]. Another reason is probably the exclusion of the subjects who showed fasting IRI value with 15 μU/mL and more than 15 μU/mL [17]. If we should include these cases into the research, several biomarkers would have shown rather scattered data, which may make difficult to lead a certain speculation in the light of glucose variability.

Similar to IGI for 75gOGTT, Delta ratio and AUC ratio of Carbo70 were proposed. When compared the both, AUC ratio of Carbo70 revealed higher coefficient correlation with related biomarkers. These results would suggest the usefulness of this marker and also this clinical application for diabetic medical practice.

Only two days LCD brought remarkable improvement of average blood glucose level and M value [15]. The latter showed more drastic change than the former. From this result, M value would be clinically useful for the evaluating the changes of glucose variability, because M value means average glucose level and MAGE [25,26].

Regarding lipid profile, triglyceride value has decreased remarkably between day 2 and day 14, with 12 days of LCD. This clinical effect has been reported and known [27].

Regarding five groups, HbA1c and M value showed the linear distribution from group 1 to 5. M value revealed clearer distant distribution than HbA1c, where the data of M value showed larger difference. This tendency would be beneficial characteristic point of M value.

In comparison of HOMA-R and HOMA-β, the latter showed clearer difference distribution from group 1 and 5. The former shows insulin resistance, and the latter shows the insulin secretion ability from β cells of the pancreas [28]. This result may suggest that decreased insulin secretion would be more involved in the glucose variability rather than insulin resistance [29].

When compared with Delta ratio and AUC ratio for Carbo70, the median value in the latter has decreased remarkably from group 1 to 5. This result would suggest the predominance of method of AUC ratio for Carbo70.

HbA1c showed significant correlation with average glucose and M value on day 2. Both showed almost same high value of R^2 suggesting the close relationship between them.

Correlations on average glucose and M value between day 2 and day 4 showed remarkably high value, with more than 0.9 of R^2. From this, we may speculate the average glucose level by only two days of LCD in figure 5a.

Recently, there are several reports of meal tolerance test (MTT). It can speculate the pancreatic function for measuring the responses of insulin and glucose [29]. One trial of MTT is a breakfast including 450 kcal and PFC = 15:35:50 [30]. In this case, it seems to have 56g of carbohydrate dose in the breakfast.

Another MTT would be the High-protein liquid meal, which has carbohydrate 33g, protein 15g, fat 6g (237 ml, Vevey, Switzerland) [31]. This PFC ratio consists of 25:20:55%, and we can speculate that Delta IGI for Carbo 33g would be 1.6 in average.

Furthermore, Park., *et al.* reported 2 types of formula breakfast as MTT [32]. They are carbo-breakfast with PFC = 15:20:65%, and protein-breakfast with PFC = 35:20:45%. They examined MTT using carbo-group and protein-group, where the latter showed higher insulin response and lower glucose increase. This phenomenon has been called 'second-meal phenomenon', which can keep controlling the glucose variability.

After the stimulation of mixed meal, there seemed to be GLP-1 induced insulin secretion [33]. By the preload of mixed meal, glucose tolerance can be decreased as the severity degree of T2DM [34]. From mentioned above, investigation of the responses of insulin and glucose would be useful for clarification of glucose variability.

This study has some limitation. There are rather clear clinical effect of LCD compared with CR, but there are various influence as to MTT because of its complex macronutrients. We would continue related research and expect the further elucidation of glucose variability.

Conclusion

In summary, we investigated 67 male patients with T2DM as to glucose variability. Providing CR and LCD, several biomarkers were measured and investigated such as average glucose, M value, Delta and AUC ratio of Carbo70. These results suggest clinical efficacy of LCD, M value, meal tolerance test, and so on for future research development.

Acknowledgement

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

Conflicts of Interest

The authors state that there are no conflicts of interest.

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