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Research Article

Urinary C-Peptide Excretion for Diabetic Treatment in Low Carbohydrate Diet (LCD)

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Abstract

Background: Arguments have continued about Low Carbohydrate Diet (LCD) and Calorie Restriction (CR). Authors have reported clinical research of LCD and Morbus (M) value.

Subjects and Methods: Subjects enrolled are 84 patients with Type 2 diabetes mellitus (T2DM), 60.9 ± 10.9 years. The protocol were as follows: 1) CR diet on day 1, 2 with 60% carbohydrates, and LCD on day 3-14 with 12% carbohydrates, 2) Daily profile of blood glucose 7 times a day on day 2 (CR) and day 4 (LCD), 3) urinary C-Peptide radioimmunoassay (u-CPR) excretion, 4) M value calculation, 5) investigation of these data with correlation.

Results: Subjects were classified into 4 groups according to M value, which were .4–21, 23–66, 29–192, 200–728, respectively. HbA1c value was 6.2, 8.0, 7.8, 9.2 %, respectively. Blood glucose in median from day 2 to day 4 were 123 to 107 mg/dL, 164 to 130 mg/dL, 193 to 156 mg/dL, 277 to 201 mg/dL, respectively. M value in median from day 2 to 4 was 6.3 to 9, 41 to 7, 108 to 16, 367 to 88, respectively. u-CPR was 88 to 58, 53 to 35, 65 to 52, 74 to 64, respectively. There were significant correlations among among glucose, M value and u-CPR.

Discussion and Conclusion: Average glucose, M value and u-CPR decreased remarkably on day 4. As average glucose and M value were higher, decrease degree were larger. These results suggested that carbohydrate in meal would influence glucose variability in T2DM. Our data would become basic data for pathophysiological analysis of glucose variability research in the future.

Keywords: Urinary C-peptide (u-CPR); Low Carbohydrate Diet (LCD); Morbus value (M value); type 2 diabetes mellitus (T2DM); Average Glucose (AG)

Abbreviation: CPR: C-Peptide immunoreactivity, **LCD:** Low-Carbohydrate Diet, **CR:** Calorie-Restricted, **T2DM**: Type 2 Diabetes Mellitus, **T1DM:** Type 1 Diabetes Mellitus, **M value:** Morbus value, **MAGE:** Mean Amplitude of Glycemic Excursions, **HOMA-R:** Homeostasis model assessment-Insulin Resistance, **HOMA-β:** Homeostasis model assessment of β-cell function.

Introduction

For years, there has been discussions concerning Low Carbohydrate Diet (LCD) and Calorie Restriction (CR). Recent reports have showed efficacy of LCD such as randomized controlled trials, systematic review and meta-analyses [1-3].

Historically, Atkins and Bernstein originally have started LCD in western countries [4,5]. Consecutively, clinical predominance of LCD have been shown by investigators [6-9]. Furthermore, LCD has been applied widely to several diseases and impaired states, such as metabolic syndrome

(Met-S), obesity, nonalcoholic fatty liver disease (NAFLD), cardiovascular disease, and so on [10-12]

On contrast, in Japan, the author have firstly introduced and reported LCD for T2DM in Japan and developed LCD in lots of opportunities [13,14]. Subsequently, we reported clinical studies concerning LCD with pathophysiological aspects [15-18].

In current study, we investigated urinary C-Peptide immunoreactivity (u-CPR) excretion in patients with Type 2 Diabetes mellitus (T2DM). Simultaneously, we measured the average glucose and Morbus (M) value, and studied the detail correlation among these biomarkers.

Subjects and Methods

In current study, the subjects included 84 patients with T2DM, which were 33 males and 51 females. They are 28-84 years old (yo) with 60.9 ± 10.9 (mean +/- SD) yo. in average, 63 yo in the median value.

Subjects were enrolled from the in-patients of the educational admission for further evaluation and treatment of T2DM. The protocol of diet therapy were as follows:

1) CR diet was provided on day 1 and 2, which had 60% carbohydrates, 25% lipids and 15% protein with 1400 kcal/day.

2) LCD was provided from 3 to 14 days, which had 12% carbohydrates, 64% lipids and 24% protein with 1400 kcal/day.

3) This LCD has been called "super-LCD formula" in our clinical research for LCD, which is one of the Very low-carbohydrate ketogenic diet (VLCKD) by the definitions of LCD [13-16].

Examinations included several kinds of glucose metabolism. The are 1) several basal biomarkers on admission, 2) daily profile of blood glucose 7 times a day on day 2 (CR) and day 4 (LCD), 3) u-CPR were measured on day 2 and day 4, 4) M value was calculated from blood glucose level.

Morbus (M) value

Data obtained from daily profile of blood glucose were calculated into Morbus (M) value. M value is the index which represents both blood sugar level and mean amplitude of glycemic excursions (MAGE) [19-22]. Regarding glucose variability, daily profiles of blood glucose has been measured 7 times a day, which data were calculated into average glucose and M value. M value has been proposed for researching average glucose and MAGE. This index has been calculated as a logarithmic transformation of the deviation of glycemia from an arbitrary assigned "ideal" glucose value. Clinically, ideal glucose level would be around 120 mg/dL, then M value uses 120 mg/dL for the standard level. Consequently, M value expresses both the average glucose value and the effect of glucose swings [19-22].

M value is calculated by the following formula: M = MBS + MW, where MW = (maximum blood glucose−minimum glucose)/20; MBS = the mean of MBSBS; MBSBS = individual M-value for each blood glucose value calculated as (absolute value of [10×log(blood glucose value/120)])3.

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

Concerning the interpretation of M value, the standard range would be <180, borderline 180-320 and abnormal >320. Adequate sampling times a day have been argued for detail and precise evaluation of glucose variability and MAGE. Similar results were found on 7 times or 20 times of sampling per day [19,22,23]. It also revealed similar results compared with the continuous glucose monitoring (CGM) [22,24].

Statistical analyses

In this study, obtained data was represented as the mean +/- standard deviation (SD) and also represented median, quartile of 25% and 75% in biomarkers. For statistical analyses, correlation coefficients were calculated using Pearson or Spearman test of the Microsoft Excel analytical tool, which is Four steps Excel Statistics 4th edition [25]. A significance level of less than 5% was considered to be statistically significant.

Ethical Considerations

This study was conducted in compliance with the ethical principles of the Declaration of Helsinki. It was also along with 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). Ethical committee meeting was held by physician, researchers, medical staff and legal expert. Informed consent was obtained from the subjects. The study was registered with UMIN #R000031211.

Results

Subjects were classified into 4 groups according to M value. Data of M value in 4 groups were, 4–21, 23–66, 29–192, 200–728, respectively (Table 1). Each group has 21 subjects, and other results of biomarkers were shown in Table 1.

	Group 1	Group 2	Group 3	Group 4
Subjects				
age (years old)	57.7±11.1	61.4±13.3	62.4±10.3	62.4±9.0
median [25% - 75%]	59 [55-63]	65 [55-69]	65 [58-69]	65 [61-68]
M/F	12/9	5/16	6/15	10/11
number	21	21	21	21
M value				
range	4 - 21	23 - 66	29 - 192	200 - 728
data of M value	8.3±4.5	42.6±12.7	120±40	401±174
median [25% - 75%]	6.3 [5.6 - 9.2]	41 [32 - 52]	108 [89 - 151]	367 [246 - 516]
Glucose metabolism				
Fasting glucose (mg/dL)	120±20	134±21	162±33	215±33
median [25% - 75%]	114 [107 - 135]	137 [121 - 143]	163 [141 - 178]	216 [207 - 240]
Fasting IRI (μIU/mL)	12.9±8.9	7.8±4.1	6.9±5.1	4.9±2.9
median [25% - 75%]	10.6 [6.7 - 16.7]	7.5 [4.9 - 8.8]	5.6 [3.9 - 11.1]	4.1 [3.1 - 7.1]
Insulin resitance				
HOMA-R	4.1±3.6	2.6±1.4	2.9±2.6	2.8±1.7
median [25% - 75%]	3.6 [2.2 - 5.0]	2.6 [1.5 - 2.9]	2.1 [1.3 - 3.9]	2.1 [1.7 - 4.2]
HOMA-β	89±46	39±21	27±19	11±6
median [25% - 75%]	80 [56 - 131]	34 [26 - 55]	21 [12 - 46]	10 [6 - 13]
lipids metabolism				
Triglyceride (mg/dL)	124±73	130±69	125±81	170±114
median [25% - 75%]	107 [72 - 133]	101 [75 - 161]	102 [72 - 155]	163 [81 - 200]
HDL-C (mg/dL)	55±16	54±14	67±19	64±17
median [25% - 75%]	52 [48 -57]	53 [44 - 65]	63 [55 - 82]	63 [56 - 68]
LDL-C (mg/dL)	121±42	134±39	128±33	138±41
median [25% - 75%]	113 [95 - 134]	132 [109 - 153]	129 [109 - 153]	141 [113 - 157]

Data are expressed mean standard deviation, and also meadian [25%-75%].

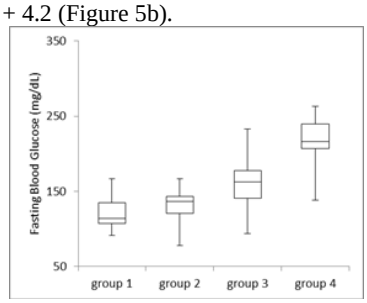
Table 1: Basal data of the subject classified into 4 groups.

Fasting blood glucose and HbA1c value increased from group 1 to group 4 in order (Figure 1). Each median value was 114, 137, 163, 216 mg/dL, and 6.2, 8.0, 7.8, 9.2%, respectively. The average glucose on day 4 was decreased from that on day 2 in 4 groups (Figure 2). Average glucose in median from day 2 to day 4 in each group was 123 to 107 mg/dL, 164 to 130 mg/dL, 193 to 156 mg/dL, 277 to 201 mg/dL, respectively.

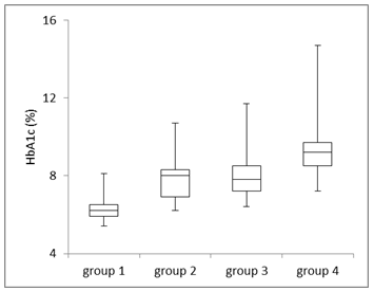
When calculated on daily profile of blood glucose into M value, it decreased from day 2 to day 4 in group 2,3 and 4 (Figure 3). M value in median from day 2 to day 4 in each group was 6.3 to 9, 41 to 7, 108 to 16, 367 to 88, respectively.

U-CPR on day 2 and day 4 are shown in Figure 4. In each group, decreased value from day to day 4 was 88 to 58, 53 to 35, 65 to 52, 74 to 64, respectively.

There is significant correlation between blood glucose in average on day 2 and day 4 ($p<0.01$) (Figure 5a). There is significant correlation between blood glucose in average and HbA1c ($p<0.01$) in which the regression curve showed $y = 0.02 x + 4.2$ (Figure 5b).

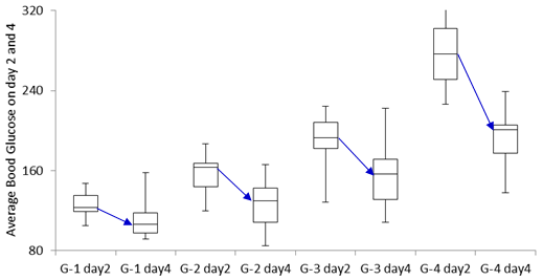


1a: Fasting blood glucose increases from group 1 to 4.



2a: HbA1c value increases from group 1 to 4.

Figure 1: Blood glucose and HbA1c in 4 groups.



G-1 day2: Group 1 on day 2 (CR), G-4 day4: Group 4 on day 4 (LCD).

Figure 2: The changes of average blood glucose on day 2 and day 4 in 4 groups.

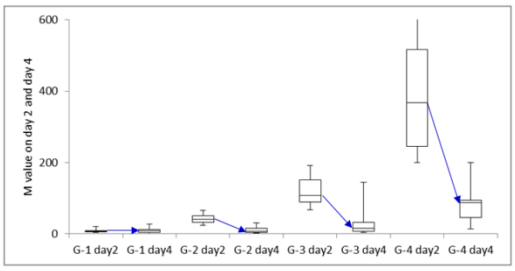
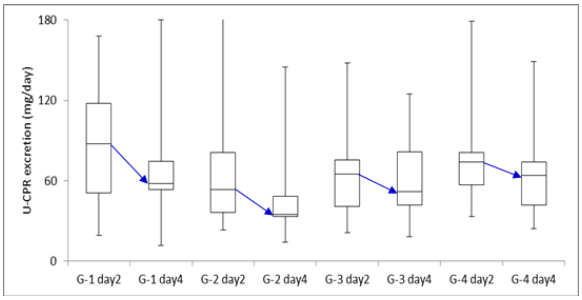
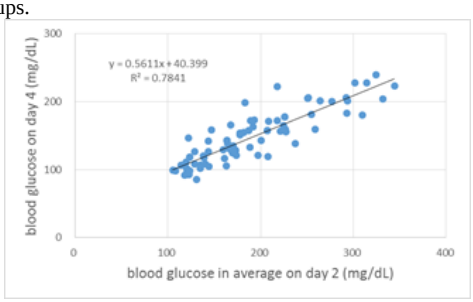


Figure 3: The changes of M value on day 2 and day 4 in 4 groups.

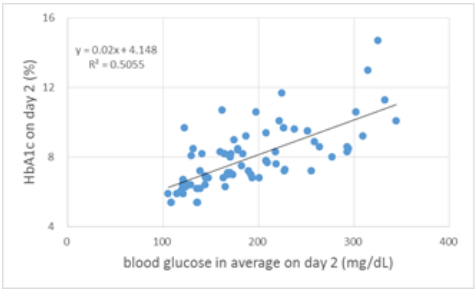


U-CPR: urinary C-peptide immunoreactivity,

Figure 4: The changes of U-CPR excretion on day 2 and day 4 in 4 groups.



5a: Correlation between blood glucose in average on day 2 and day 4.

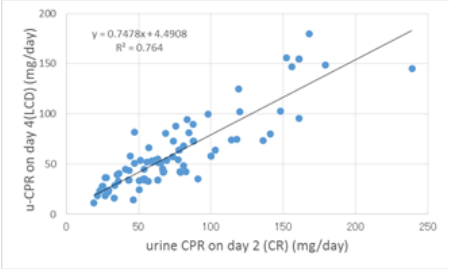


5b: Correlation between blood glucose in average and HbA1c.

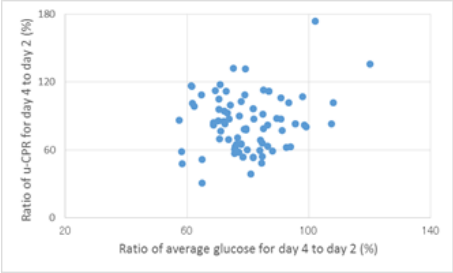
Figure 5: Correlation between blood glucose and HbA1c.

Significant correlation was observed between u-CPR on day 2 (CR) and day 4 (LCD) ($p<0.01$), in which the regression curve showed $y=0.75x + 4.5$ (Figure 6a). There is no significant correlation of ratio for day 4 to day 2 between average glucose and u-CPR (Figure 6b).

There is significant correlation between M value on day 2 and day4 ($p<0.01$) (Figure 7a). There is no significant correlation of ratio of day 2 and 4 between M value and u-CPR (Figure 7b).

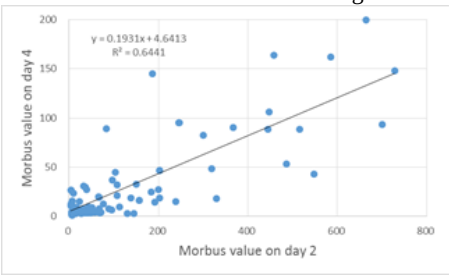


6a: Correlation between u-CPR on day 2 (CR) and day 4 (LCD).

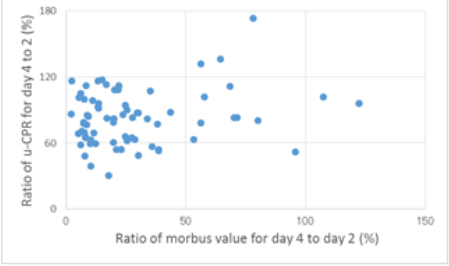


6b: Correlation of ratio for day 4 to day 2 between average glucose and u-CPR.

Figure 6: Correlation of u-CPR and blood glucose.



7a: Correlation between Morbus (M) value on day 2 and day4.



7b: Correlation of ratio of day 2 and 4 between M value and u-CPR.

Figure 7: Correlation between Morbus (M) value and u-CPR.

Discussion

Recently, fundamental and clinical research of LCD have been developed and prevalent [26,27], and we have continued research for LCD with proposal for medical practice [28-30].

In this study, we examined changes in average glucose, M value, urinary CPR in 2 days after diet changed from CR to LCD. We also investigated the correlation among these biomarkers, and clarified efficacy of LCD for the improvement of the profile of blood glucose in short period.

M value has been useful marker that would evaluated elevated blood glucose and increased MAGE. In this diabetic research field, we have continued to study the detail of glucose variability using M value [18,30,31].

As for current study, we divided into 4 groups according to M value. Group 1 was mild, and group 4 was severe in degree of diabetes. In Groups 2, 3 and 4, mean glucose and M values clearly decreased from day 2 to 4. On contrast, group 1 includes mild diabetes or pre-diabetic subjects. In other words, it seems that blood glucose and HbA1c are close to normal people, and the insulin secretion ability is preserved proportionally.

In group 1, blood sugar in median decreased from 123 to 107 mg/dL, and u-CPR decreased remarkably from 88 to 55 mg/day. For meal protocols, CR for day 1, 2. and LCD for day 3,4 were provided. In comparison of day 2 and day 4, the carbohydrate ratio is 60% vs. 12%, the carbohydrate amount per day is 210 g vs. 42 g. This difference in carbohydrate intake possibly leads to lowering of blood glucose and lowering of CPR in urine, with mutual correlation.

Average glucose decreased in group 1 from day 2 to day 4, but the M value did not decrease. The reason would be that the M value is calculated with the absolute value of blood glucose away from 120 mg / dL, which is ideal blood glucose level.

Actually, several cases in group 1 showed almost normal range of blood glucose at day 2. These cases developed decreased blood glucose around 80-100 mg/L at day 4. That is why M value in group 1 did not decrease from day 2 to day 4 [32,33].

In the protocol of this study, diet therapy was changed from CR to LCD for T2DM. Among them, the main investigation were u-CPR measurements in 2 days apart, and it was possible to analyze the relationship with mean blood sugar and M value simultaneously. As a result, the reduction in carbohydrate intake decreased blood glucose level and glucose fluctuation, especially leading to a drastic decrease in M value.

In addition, insulin secretion was suppressed due to a decrease in blood glucose spike, leading to decreased u-CPR excretion which is an indicator of insulin secretion. From the above, it can be said that the series of pathophysiological pathway in diabetes has been improved in the short term. These results suggest that LCD would have remarkable efficacy for nutritional treatment of diabetes.

Significant correlation between blood glucose in average and HbA1c ($p<0.01$) was observed. Its regression curve would indicate that HbA1c (%) = 0.02 x AG (mg/dL) + 4.2. When x axis and y axis changes each other, the equation becomes “AG = 25.3 x HbA1c – 12.2”.

Well-known equation has been reported by Nathan et al. which was “AG = 28.7 x HbA1c – 46.7” analyzed from 2700 samples [34]. As a comparison, substitute HbA 1 c = 7, 8, 9% into our formula and Nathan's formula. Then, the result is 165.1 vs 154.2 mg / dL, 190.2 vs 182.9 mg / dL, 215.5 vs 211.6 mg / dL, and both estimated values are near and compatible.

We measured average blood glucose 7 times a day. It is said that the difference from the measurement of 20 times

in the past is small and that the reliability is actually high. The subjects in this research were 84 cases of type 2 diabetes, including cases where HbA1c was low. Several cases in group 1 may showed lower HbA1c and blood glucose may be a higher than that of normal subjects which has the same HbA1c level.

On the other hand, study by Nathan et al. included type 1 diabetes, type 2 diabetes and normal individuals. Therefore, in regions where HbA1c is low, blood sugar levels are expected to be lower because there are many samples of normal subjects. Actually, if we enter 6% as HbA1c level into both formulas of ours and Nathan, data would be 139.6 mg/dL vs 125.5 mg/dL.

U-CPR has been a simple and useful test in the diagnosis of diabetes [35]. It has been said that u-CPR and serum CPR has been said to be highly correlated [36]. Recently, measurement of u-CPR with creatinine would be recommended for more accurate result [37,38]. .

C-peptide is clinically simple, noninvasive and useful examination for diabetes. Its application would be spreading in various situation, such as outpatient, in-patients and postprandial measurements [39-41].

Conclusion

In this study, we reported the changes in average glucose, M value and urine CPR value after meal change from CR to LCD. Associated with several correlation among them, and our results would become basic data for pathophysiological analysis of glucose metabolism of future research.

Acknowledgement

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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