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 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)


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 would be <180, borderline 180-320 and abnormal >320. Concerning the interpretation of M value, the standard range would be <180, borderline 180-320 and abnormal >320.

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.

M-value=\frac{\sum_{i=1}^{n} MBS_i}{N} + \frac{W}{20} \quad \text{where} \quad MBS_i = \frac{10 \log(blood\ glucose\ value/120)}{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].

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).
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.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

