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Investigation of C-peptide Index for Carbo70 by the severity of diabetic state

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Abstract

Background: Authors and colleagues have reported nutritional research so far concerning Low Carbohydrate Diet (LCD). Formerly, we proposed useful method for insulin response to 70 g of carbohydrate. Similarly, C-peptide index for Carbohydrate-70 (CPI-Carbo70) is studied and proposed in this report.

Subjects and Methods: Subjects enrolled were diabetic patients that were divided into three groups due to diabetic severity. Among them, average HbA1c was 6.6%, 7.8%, 10.0% in low, middle, high group, n=15, 15, 16 respectively. As in-patients, they were on Calorie Restriction meal on day 1 and 2, which has 1400kcal/day with carbohydrates 60%, lipids 25%, protein 15%. On day 2, breakfast with carbohydrate 70 g was provided, and glucose and C-peptide levels were measured at 0, 30 minutes.

Results: Biomarkers were analyzed in 3 groups. Increment C-peptide (CP) and CPI-Carbo70 in 3 groups were 0.58, 0.57, 0.27 and 2.1, 3.2, 1.2, respectively. As for M value, CP increment, CP on 30 min, CPI-Carbo70 was investigated, which were lower in high group. There is significant correlation between HbA1c and CPI-Carbo70 ($p<0.05$).

Discussion and Conclusion: CPI-Carbo70 may be useful for evaluating pancreas function and glucose variability. These data could be basal and useful in the light of clinical evaluation and further research development.

Keywords: C-peptide index for Carbohydrate-70 (CPI-Carbo70); Insulinogenic index (IGI); Calorie Restriction (CR); C-peptide (CP); Type 2 diabetes mellitus (T2DM)

Introduction

Metabolic syndrome (Met-S) has been increasing and become the important problem in developed and also developing countries [1]. It includes several influencing factors such as lifestyle, age, meal, exercise, habitual status, socioeconomic status, and others [2]. From pathophysiological aspect, Met-S has basically insulin resistance and close relationship of developing diabetic status with macroangiopathy and microangiopathy [3].

The number of diabetic patients in almost region of the world has been increased [4]. As to diabetic practice, there has been recently a large paradigm changes. The proposal of change in standard value about HbA1c was presented by American College of Physicians (ACP) [5]. The important point for the primary care physicians was that the management goal for HbA1c in most type 2 diabetic patients would be 7% or more and less than 8%. In response to this statement, American Diabetes Association (ADA) showed the comments concerning the goals and treatment for diabetes associated with complications of cardiovascular disease and the prevention of recurrence in the treatment for diabetes [6].

Furthermore, there is "The Prospective Urban Rural Epidemiology (PURE) study", which is known as multi-centered epidemiological study. It has covered large-scale area with 18 countries worldwide [7]. It showed that total mortality risk was increased with increased intake of carbohydrate (HR 1.28). Then, carbohydrate was recommended to be reduced for healthy daily living [8].

A standard of Medical Care about Diabetes was proposed recently, by International Diabetes Federation (IDF) [9]. Among them, important aspects were checking intake and counting for carbohydrate amount with experience-based evaluation. Study of macronutrient and eating methods may be useful for better glucose control.

On contrast, various discussions on diabetic nutritional therapy have been continued, mainly Low Carbohydrate Diet (LCD) and CR [10-12]. LCD was started by Atkins and others in North American and European region and was developed widely [13]. Similarly, The author started LCD in Japan, and have treated and reported about its clinical effects [14]. In addition, we have proposed useful and simple formula diet of LCD, with elevated ketone bodies, renal function, hyperlipidemia and M value [15-17].

Through our consecutive investigation concerning CR and LCD, we proposed new index that is simple and useful method. Similar to 75 g oral glucose tolerance test (75 g OGTT) and insulinogenic index (IGI) to carbohydrate 75 g, we came to take advantage of breakfast of CR including 70 g of carbohydrate. Corresponding to IGI-75 g OGTT, IGI-Carbo70 was proposed and its clinical usefulness was investigated

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[18]. Along to this research direction, c-peptide index at 0-30 minutes for Carbo70 was studied in this study.

Subjects and Methods

Enrolled subjects were type 2 diabetes mellitus (T2DM) and were divided into three groups due to the severity of the diabetic state. Three groups were called low, middle, high group, associated with the data that average HbA1c value was 6.6%, 7.8%, 10.0%, and number of the cases was 15, 15, 16, respectively.

Methods are performed in the hospital. Diabetic cases were admitted for 2 weeks for detail evaluation treatment. They were on our protocol of CR and LCD nutritional therapy as in-patient. The details of the methods are described as follows: 1) CR diet was given to diabetic patients on day 1-2. CR had 1400 kcal/day and its PFC was 15%, 25%, 60%, respectively. 2) LCD was given on day 3-14, including 1400 kcal/day with the PFC=24%, 64%, 12%, respectively.

As mentioned above, both protocol with CR and LCD was continued for years in our clinical research. In current study, however, we have used only the breakfast on day 2. CR meal includes 840 kcal a day from carbohydrate including totally the mount of carbohydrate 210g in three meals. It is from the nutrients balance of PFC by the standard guideline for Japan, which is proposed from Japan Diabetes Society (JDS) [19]. In this way, formula breakfast meal has provided to the subjects after overnight fasting, which contains carbohydrate 70 g in it.

The precise protocol of the study is in the following: 1) fundamental biomarkers were checked in early morning on day 2, 2) Blood levels of glucose and C-peptide were measured before breakfast (0 min), 3) patient eats breakfast including carbohydrate 70 g, 4) glucose and C-peptide were measured 30 minutes after breakfast, 5) values of 0 min, 30 min and increased value of blood glucose and C-peptide were measured, 6) index of ratio for increased value (increment) of C-peptide / glucose was investigated and analyzed, which is CPI-Carbo70.

Profile of blood glucose and Morbus value

Regarding profile of blood glucose on day 2 was checked 7 times a day, that is, 8, 10, 12, 14, 17, 19, 22 h. From these, we calculated the blood glucose in average and M value.

M value has been known as the useful index indicating two factors, which are blood glucose value and the mean amplitude of glycemic excursions (MAGE) [20,21]. After obtaining the data of profile of glucose, we can calculate glucose level in average and M value. M value was proposed for researching the status of MAGE. This index is characteristic for a logarithmic transformation of the deviation of blood glucose from an arbitrary assigned "ideal" glucose value. It includes the degree of mean glucose value and glucose swings [20-22].

The definition of M value is shown. 1) $M=M^{BS} + M^{W}$: M value is the total of M^{BS} and M^{W}. 2) M^{W} is maximum blood glucose − minimum glucose)/20. 3) M^{BS} is the mean of MBSBS. 4) MBSBS is the individual M-value for each blood glucose value, that is calculated as (absolute value of $[10 \times \log (\text{blood glucose level}/120)])^3$ [20-22].

For M value, the interpretation would be in the following. 1) Less than 180 is normal or standard, 2) the range between 180 to 320 is borderline, 3) more than 320 are abnormal. As several experimental researches, similar results were obtained on 7 times or 20 times per day [21-23]. These results revealed almost similar, when it is compared with that of continuous glucose monitoring (CGM) [21,22,24].

Statistical analysis

The results of this study were revealed by 2 ways. One is represented by the mean ± standard deviation (SD), and another is by the median, quartile of 25% and 75% according to the biomarkers. For the investigating the results statistically, we used the correlation coefficients which were calculated according to the Spearman test. The reference method was used on the analytical standard tool [25].

Ethical standard

This research was conducted in compliance with the ethical principles based upon the Declaration of Helsinki, where additional commentary was done in 2004 General Assembly Tokyo, Japan. It was also conducted with Personal Information Protection Law and in reference to "Standards for the Implementation of Clinical Trials (GCP), an ordinance of the Ministry of Health, Labour and Welfare No. 28 of March 27, 1997, as well as "Ethical Guidelines for Epidemiology Research" by the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare.

Furthermore, we have established an ethical committee including doctor, nurse, pharmacist and expert in the medical and legal specialty. We have discussed and made confirmation that current study is valid and agreed with all members without any problems. Moreover, informed consents and written paper agreements have been obtained from the subjects. Current study was also registered in the open database (UMIN) run by National University Hospital Council of Japan (Test ID: #R000031211).

Results

1. Basal data

In 3 groups, basal data were summarized in **Table 1**, in which each value is shown by average and standard deviation. Average glucose and Morbus (M) value in 3 groups was 168 mg/dL, 197 mg/dL, 243 mg/dL, and 82, 124, 329, respectively.

2. C-peptide index for Carbo70

Responses of biomarkers for C-peptide index for Carbo70 are summarized in **Table 1**, in which each value is shown by average and standard deviation. Increment of C-peptide in 3 groups was 0.58, 0.57 and 0.27, respectively.

3. Comparison of biomarkers in 3 groups

As to the comparison of 3 groups, HbA1c level and average blood glucose level are shown in **Figure 1**. Median value increased in the order of group 1,2,3. Similarly, M value in 3 groups showed rather larger differences than those of HbA1c and average blood glucose **(Figure 2)**. In 3 groups, CP increment from 0 to 30 min and CP level at 30 min are shown in **Figure 3**. High group indicated lower median value than others in both. **Figure 4** showed C-peptide index for Carbo70 in 3

	Group 1	Group 2	Group 3
Subjects			
Number (M/F)	15 (7/8)	15 (9/6)	16 (3/13)
Age(Years old)	62.0 ± 12.2	61.7 ± 11.4	63.9 ± 10.1
Glucose Profile			
HbA1c(%)	6.6 ± 0.5	7.8 ± 03	10.0 ± 1.5
Average glucose (md/dL)	168 ± 42.5	197 ± 34.3	243 ± 89.9
Morbus value	82.1 ± 93.2	124 ± 78.1	329 ± 342

Table 1: Subject and basal data.

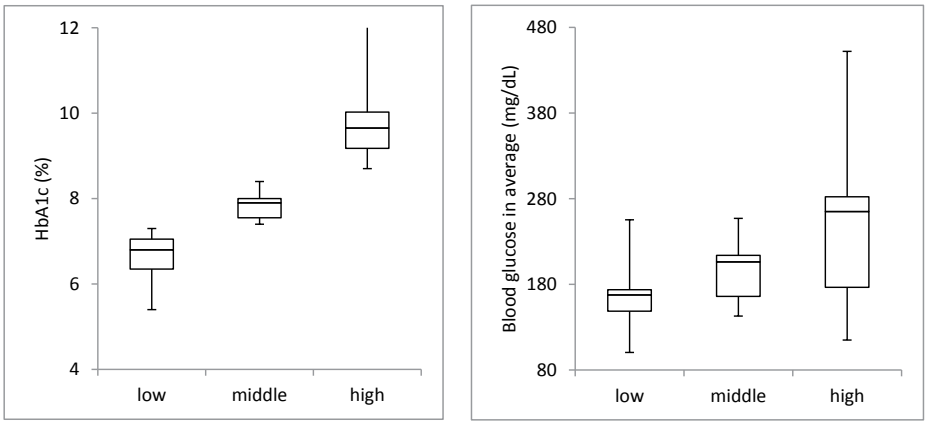

Figure 1: HbA1c and blood glucose levels in 3 groups.

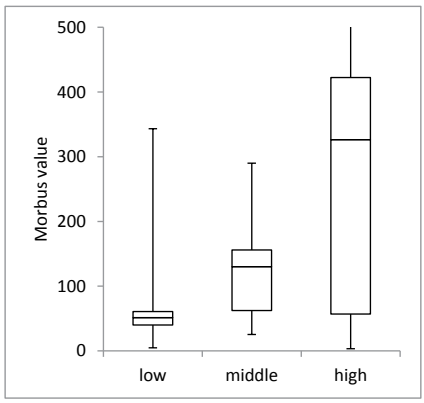

Figure 2: Morbus (M) value in low, middle and high groups.

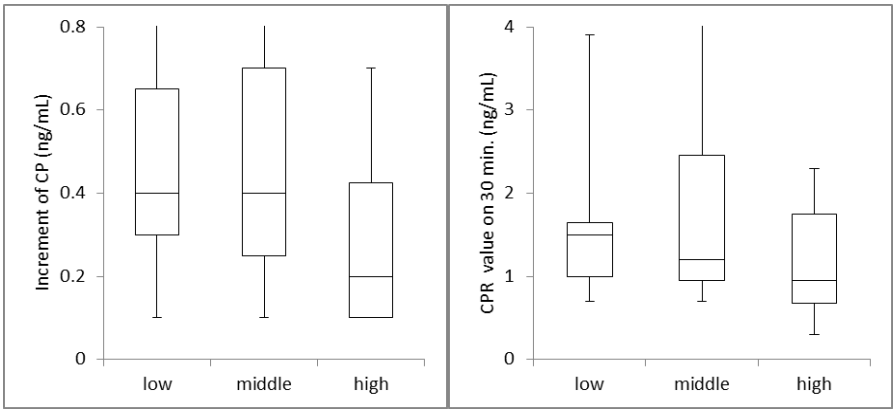

Figure 3: CP increment and CP level at 30 min in 3 groups.

groups. The median value was about 0.4 in low and middle groups, and about 0.2 in high group.

4. Correlation among CPI-Carbo70, HbA1c and M value

There is significant correlation between CPI-Carbo70 and HbA1c ($p<0.05$) **(Figure 5)**. The statistical precise data were that r=-0.382, p=0.010, n=46. Then it is nearly close to $p< 0.01$.

On the other hand, there is no significant correlation between CPI-Carbo70 and M value **(Figure 6)**. The statistical precise data were r=0.274, p=0.065 and n=46. As p value is 0.065, it is very close to 0.05.

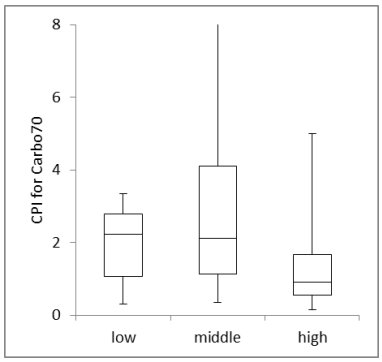

Figure 4: C-peptide index for Carbo70 in 3 groups.

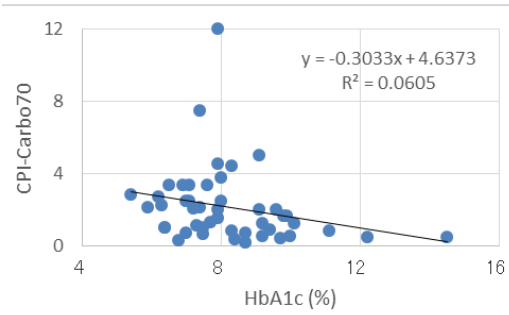

Figure 5: Correlations between CPI-Carbo70 and HbA1c. Significant correlation with r= -0.382, p=0.010.

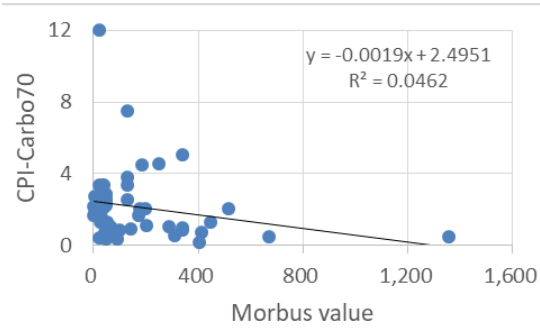

Figure 6: Correlation between CPI-Carbo70 and M value
No significant correlation with r= -0.274, p= 0.065.

Discussion

In the clinical practice, the responses of IRI and CPR against 75 gOGTT have been used for long [26]. Examination of 75 gOGTT was performed to 525 persons and blood sugar was measured in detail [27]. Half of 262 people were monophasic peaks of blood glucose, with the peaks of IRI, C-peptide (CP) at 1-1.5 hours. 0 - 30 minutes of CP increased from 0.75 to 2 nmol / L. There was a follow up study with prediabetes patients (n=406) for 9 years [28]. As a result, subjects with a 30 min post-load glucose ≥ 165 mg/dL and a 30-min C-peptide < 5 ng/mL showed 8.83 times greater risk of developing diabetes than other subjects. People in Asia can decrease the degree of postprandial hyperglycemic state from ingestion of rice, by the intake of mixture macronutrients of protein, fat and carbohydrate [29].

There are study of difference of glucose, sucrose and honey. In diabetics, the increase in the level of C-peptide after honey was not significant in comparison with either glucose or sucrose [30]. One of the interesting study is about famous Japanese fast food. The meal is a rice bowl topped with beef, and it was provided to healthy subjects with the investigation of postprandial hyperglycemia [31]. It includes protein 18.4 g, fat 20.9 g and carbohydrate 82.9 g, and glucose was elevated 65 mg/dL during 0-30 min.

From these reports, loading exam of glucose 75g and also meals for increasing glucose and CP would be useful in the clinical setting.

There have been several reports concerning postprandial hyperglycemia. The continued dietary guidance to eat vegetables before staple foods has led to the decrease of HbA1c in patients with diabetes and the prevention of the progression of diabetic complications [32]. In order to inhibit a postprandial hyperglycemia, it is recommended to add dietary fibers before taking noodles and carbohydrate food [33]. Furthermore, it has been reported that vinegar and olive oil have an inhibitory action on postprandial hyperglycemic states [34].

According to the result of a meta-analysis, dietary habit of eating a portion of yogurt everyday reduces the risk of T2DM [35]. Therefore, the dietary habit to continuously eat yogurt together with a meal possibly alleviates glycative stress by inhibiting a postprandial hyperglycemic state and contributes to the prevention of aging and the progression of age-related diseases [36].

There are many different meal habits worldwide. Especially, Asian people often take large amount of rice and crops as a starchy food. It tends to induce a rapid postprandial hyperglycemic state [37]. Furthermore, successive response of insulin surge would cause the onset of diabetes [38]. As a result, the number of diabetic patients is increasing including 73 million in India and 110 million in China [4]. Under such circumstances, scrutiny for diabetes and 1st, 2nd, and 3rd prevention are important, and it is possible that CPI-Carbo70 of this study can be used in clinical setting.

In this study, the subjects were divided into 3 groups, with obvious differences in HbA1c, mean blood glucose and M value. There was no obvious difference in blood glucose rise in 3 groups. The degree of increase in CP was about half in the high group compared to middle and low groups. In the median value, it was 0.4 ng / mL in the low and middle groups and 0.2 ng / mL in the high group. On contrast, CP value on 30 min was decreased in the order of low, middle, high in the 3 groups. From the above, the difference in the result value between the low and middle groups seemed to be not so remarkable, while the reactivity of CP in the high group seemed to show low tendency in comparison with those of other 2 groups.

There was a significant correlation between elevated blood glucose and elevated CP at 0-30 minutes. Although the differences were not obvious in the three groups, the correlation between rise value in blood glucose and CP elevation was strong in each case. This suggests the significance and usefulness of our protocol including carbohydrate burden doses and serum concentration of CP on 3 and 30 minutes.

In addition, a significant negative correlation ($r = -0.38$, $p<0.01$) was observed between HbA1c value and CP Index for Carbo 70. As HbA1c value increased, CP index for Carbo70 decreased. These results suggest that CP-index for Carbo70 would be useful marker and would become the basic data for future development of this area. As the correlation between M value and CP Index for Carbo70, r=-0.274 and

p=0.065 were found, where the relation is nearly p<0.05, and future investigation with more cases would be planned.

Regarding the significance of CP Index for Carbo70, there are some limitation concerning the various mixtures of nutrients of meal, different ingestion speed of the subject and unstable responses of insulin and C-peptide secretion. However, CP Index for Carbo70 would be one of the ideas for medical diabetic practice and research.

Conclusion

In summary, response of blood glucose and CP for carbohydrate 70 g was investigated and C-peptide Index for Carbo70 (CPI-Carbo70) was proposed. This new way may be one simple and useful for evaluating pancreas function and glucose variability. Current report would become one of the basal data in this clinical research leading to future development.

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