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Study on responses of C-peptide and blood glucose for Carbohydrate 70g in diabetes

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Abstract

Background: Discussion concerning Carbohydrate Restriction (CR) and Low Carbohydrate Diet (LCD) has been continued. Authors formerly proposed insulinogenic index-carbohydrate 70 g (IGI-carbo70). Along this, C-peptide index for Carbohydrate-70 g (CPI-Carbo70) is studied.

Subjects and Methods: Subjects were 46 patients (62.5 yo. in average) with Type 2 diabetes mellitus (T2DM) and admitted for evaluation. CR diet was given on day 1-2 with 60% carbohydrates, 25% lipids and 15% protein with 1400 kcal/day. On day 2, breakfast with Carbo70 was given, and glucose and C-peptide (CP) were measured at 0 and 30 minutes and analyzed.

Results: As basal data, average HbA1c was 8.1%, median HbA1c, average daily glucose, median M value was 7.7%, 187 mg/dL, 71, respectively. In response to Carbo70, median values of glucose-0, glucose-30, delta-glucose, CP-0, CP-30, delta-CP was 142, 186, 22 mg/dL, 0.9, 1.4, 0.4 ng/mL, respectively. CPI-Carbo70 was 1.54 in median. There were significant correlation between glucose and CP on 0, 30min, delta-0-30min ($p<0.01$). Significant correlation was observed between CPI and HbA1c, CPI and M value ($p<0.01$).

Discussion and Conclusion: CPI-Carbo70 might be useful for evaluating pancreas function and glucose variability in clinical research. Current data would become the fundamental data for the future diabetic practice and research development.

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

Abbreviations: CR: Carbohydrate Restriction; LCD: Low Carbohydrate Diet; CPI-Carbo70: C-peptide index for Carbohydrate-70 g; T2DM: Type 2 diabetes mellitus; ADA: American Diabetes Association; ACP: American College of Physicians; IDF: International Diabetes Federation; 75 g OGTT: 75 g oral glucose tolerance test; IGI-Carbo70: insulinogenic index (IGI)-Carbohydarate70 g; M: Morbus value; MAGE: mean amplitude of glycemic excursions.

Introduction

Metabolic syndrome (Met-S) has been prevalent in the world nowadays. It was proposed and investigated from syndrome X in 1980s associated with insulin resistance [1]. Met-S has been gradually increased with medical, social and economic problems [2], and it is also defined as a cluster of mutual metabolic abnormalities accompanied by glucose metabolism, including dyslipidemia, elevated blood pressure and central obesity [3].

As mentioned above, impaired glucose metabolism would exist in the fundamental pathophysiology of Met-S. Patients with diabetes mellitus have been increasing worldwide [4]. There was recently the changes in the guideline concerning diabetes. American Diabetes Association (ADA) gave comments in 2017 [5], which was followed by the joint algorithm of European Diabetes Society (EASD) 2012 [6]. After that, American College of Physicians (ACP) proposed the change in standard value about HbA1c [7], in which the

management goal for HbA1c in most type 2 diabetic patients would be 7% or more and less than 8%. Against the concept of ACP, ADA made an objection comment immediately [8]. Thus, diabetic management has been in discussion among several guidelines from medical societies, leading to better clinical practice with accumulated evidences.

Moreover, there was a large-scale epidemiological study, which is "The Prospective Urban Rural Epidemiology (PURE) study". It included wide data from 140 thousands subjects from 17-18 countries in the world [9]. The result revealed that there were higher carbohydrate intake associated with an increased risk of HR 1.28 of total mortality. Then, it seems to be recommended to take lower carbohydrate for everyone to lead a better life [10].

International Diabetes Federation (IDF) summarized and proposed the Standards of Medical Care in Diabetes [11]. Among this guideline, the crucial points seemed to be monitoring carbohydrate intake, carbohydrate counting and experience-based estimation. In the future, continuing evaluation and investigation of eating patterns and macronutrient distribution would be beneficial for achieving better glycemic control.

Regarding the nutritional treatment for diabetes mellitus, there has been continuing discussion the comparison about Calorie Restriction (CR) diet and Low Carbohydrate Diet (LCD) [12,13]. Originally, LCD was initiated by Bernstein who was physician with type 1 diabetes mellitus (T1DM). After that, LCD became rather popular and known widely [14]. In Japan, authors and colleagues have started LCD and developed medically and socially with Japan LCD promotion association, and have given adequate therapy for many diabetic patients with successful treatment [15]. Furthermore, we have continued LCD research related to lipid metabolism, renal function, elevated ketone bodies and three types of LCD formula which are petit, standard and super LCD [16-18].

As we have continued clinical research about CR /LCD, and related investigation, we have proposed a trial of clinically new index which is simple and useful method. It is similar procedure and calculation of insulinogenic index (IGI) to 75 g oral glucose tolerance test (75 g OGTT). Subjects have breakfast including 70 g of carbohydrate, and blood samples are drawn before and 30 minutes after for the measurement of blood glucose and immunoreactive insulin (IRI) [19]. It is called insulinogenic index (IGI)-Carbohydarate 70 g (IGI-Carbo70), and seems to become useful for clinical diabetic practice.

We develop this evaluation method, try to use the measurement of C-Peptide (CP) value instead of IRI and report the data in this study.

Subjects and Methods

In current study, the subjects were 46 patients (M/F 19/27) enrolled with Type 2 diabetes mellitus (T2DM). Fundamental data were shown in Table 1. Average age is 62.5 +/- 10.9 years old (mean +/- standard deviation) and 65 (55- 68) years old (median [25-75%]). They were admitted to the hospital for 14 days, which purpose would be further evaluation, examination and treatment. They were in-patient and on our protocol of CR and LCD nutritional therapy.

Methods are described in the following: 1) Formula diet for CR was given to the subjects on day 1 and 2. CR includes 60% carbohydrates, 25% lipids and 15% protein with 1400 kcal/day. 2) Formula meal of super LCD was provided from 3 to 14 days, including 12% carbohydrates, 64% lipids and 24% protein with 1400 kcal/day.

This protocol with CR and LCD has been continued in our clinical research for years. However, this study has only indicated for the breakfast on day 2. Formula CR meal has 840 kcal of carbohydrate per day including 210g of carbohydrate totally in 3 meals. According to the guideline of Japan Diabetes Society (JDS), standard nutrients balance of PFC (protein, fat, carbohydrate) are 60% carbohydrates, 25% lipids and 15% protein [20]. In this manner, formula breakfast including 70g of carbohydrate was provided after overnight fasting.

Detail protocol is shown as follows: 1) Basal biomarkers were checked in fasting situation on day 2, 2) blood glucose level and C-peptide value were measured before breakfast (0 min), 3) patient eats breakfast with 70 g of carbohydrate, 4) levels of glucose and C-peptide were measured 30 minutes after breakfast, 5) both markers on 0, 30 min and increment of glucose and C-peptide were measured, 6) the index of ratio for increment of C-peptide / glucose was calculated as CPI-Carbo70, 7) The detail calculation method is as follows: Increment is described by delta, delta-glucose and delta-CP are calculated, delta-CP/delta-glucose x 100 equals CPI-Carbo70.

Morbus value and glucose profile

As to the daily glucose profile on day 2, blood glucose was measured 7 times a day, which time was 8, 10, 12, 14, 17, 19, 22 h. From these data, average glucose level and Morbus (M) value were calculated.

M value has been known the useful index which indicates both blood sugar level and mean amplitude of glycemic excursions (MAGE) [21,22]. From the glucose profiles, average glucose level and M value could be calculated. M value is useful for supposing the status of MAGE. M value is characteristic for a logarithmic transformation of the deviation of glycemia from an arbitrary assigned "ideal" glucose value. It includes the degree of mean glucose value and glucose swings [21-23].

The definition of M value has been as follows: 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 [21-23].

The significance and interpretation of M value has been in the following: the standard range is <180, borderline is 180-320 and abnormal range is >320. According to some experimental research, similar results were taken for measuring 7 times or 20 times a day [22- 24]. Furthermore, its

revealed similar result compared with continuous glucose monitoring (CGM) [22,24,25].

Statistical analyses

In this study, data were indicated as the mean +/- standard deviation (SD) and also as median, quartile of 25% and 75% according to the biomarkers. In statistical analyses, correlation coefficients were calculated by using Spearman test of the Microsoft Excel analytical tool, which is Four steps Excel Statistics 4th edition [26].

Ethical considerations

This investigation was conducted in compliance with the ethical principles of the Declaration of Helsinki. It was also conducted 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).

In addition, an ethical committee was established including doctor, nurse, pharmacist and expert in the medical and legal specialty. We have discussed enough and got the conclusion that this this study has been valid and agreed without any problems. Furthermore, informed consents and written paper agreements have been obtained from the all subjects. The study has been registered with UMIN #R000031211.

Results

Basal data

Current study enrolled 46 patients with T2DM. Fundamental diabetic data were shown in **Table 1**. Average glucose level was 205 mg/dL and median M value was 71.

Table 1 Subjects and basal data.

	Mean ± SD	Median [25-75%]
Subjects number (M/F)	46 (19/27)	46 (19/27)
age (years old)	62.5 ± 10.9	65 [55-68]
Glucose profile		
HbAlc (%)	8.1 ±1.8	7.7 [7.0-9.2]
average glucose (mg/d1.)	204 ± 71.2	187 [161-228]
Morbus value	187 ± 256	71 [43-203]

C-peptide index for Carbo70

Responses of blood glucose and C-peptide (CP) for carbohydrate 70 g were shown in **Table 2**. The values are expressed by average +/- standard deviation and median [25%-75%]. As median value, delta-glucose, delta-CP, CPI-Carbo70 was 22 mg/dL, 0.4 ng/mL, 1.54, respectively.

Table 2 Responses of Glucose and C-peptide for Carbo-70.

	Mean ± SD	Median [25-75%]
Response of blood glucose before (0 min)	163 ± 54.9	142 [134-186]
after (30 min)	195 ± 65.2	186 [155-214]
increment (∠)	322 ± 26.4	22 [13-46]
Response of C-peptide before (0 min)	1.08 ± 0.65	0.9 [0.7-1.4]
after (30 min)	1.52 ± 0.83	1.4 [1.0-1.9]
increment (∠)	0.44 ± 0.41	0.4 [0.8-2.5]
Index of CRP for carbo-70		
ACPR/ABG	1.94 ± 1.51	1.54 [0.8-2.5]

Correlation among biomarkers

There was significant correlation between fasting glucose and C-peptide ($p<0.01$) **(Figure 1)**. In response to the loading of carbohydrate 70g, blood glucose and C-peptide were measured at 30 min. There was significant correlation between glucose and-C-peptide on 30 min ($p<0.01$) **(Figure 2)**.

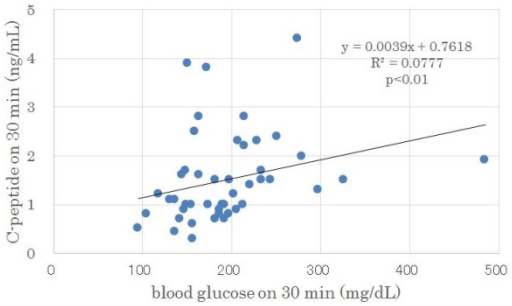

Figure 1 Correlation between Fasting glucose and C-peptide.

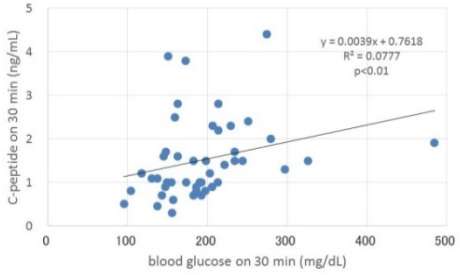

Figure 2 Correlation between glucose and C-peptide on 30 min.

C-peptide Index (CPI) is calculated by delta-CP/delta-glucose x 100. There was significant correlation between delta-CP and delta-glucose ($p<0.01$) **(Figure 3).**

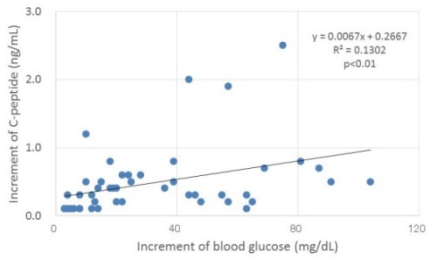

Figure 3 Correlation between delta-glucose and delta-C-peptide on 0-30 min.

Regarding CPI, two correlations were investigated. Significant negative correlation was observed between CPI and HbA1c (p<0.01) **(Figure 4)**. Furthermore, significant negative correlation was observed between CPI and M value (p<0.01) **(Figure 5)**.

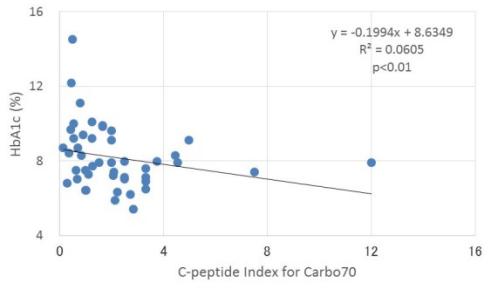

Figure 4 Correlation between HbA1c and CPI-Carbo70.

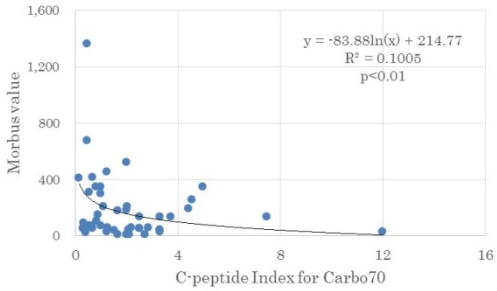

Figure 5 Correlation between M value and CPI-Carbo70.

Discussion

Authors and colleagues have continued clinical practice and research concerning LCD for years [17,18,27]. Furthermore, we have developed social movement for healthier life through Japan Low Carbohydrate Diet Promotion Association.

In this study, 70 g of Carbohydrate as a breakfast was used. **Figures 1-3** revealed 3 significant correlations between glucose and C-peptide in 0 min, 30 min, and delta-0-30min. These high correlation seems to suggest the validity and usefulness of this protocol. These statistical precise data in this order (0 min, 30 min, delta-0-30min) was r=0.395 / p=0.0078, r=0.431 / p=0.0038, r=0.510 / p=0.0005, respectively. Among these, delta-0-30min showed higher correlation degree, supposing that delta-glucose and delta-CP may be useful and meaningful in clinical practice and research.

Furthermore, **Figures 4 and 5** revealed significant correlations between CPI-Carbo70 and HbA1c, CPI-Carbo70 and M value, in which the latter revealed higher degree of correlation. When compared the difference of numerical values in HbA1c and M value, the latter has larger difference result than that of the former. Consequently, it may be more useful by M value for analyzing biomarkers in related research.

In relation to current study, there have been several reports concerning the responses of glucose, insulin and C-peptide against carbohydrate loading on breakfast.

There was a study of postprandial hyperglycemia (PPHG) after lunch and dinner in the case of with and without breakfast [28]. The result was that skipping breakfast increases PPHG with impaired insulin response and lower incremental GLP-1. It may suggest the influence of breakfast on glucose regulation that persists throughout the day. Without breakfast, AUC of blood glucose (0-30 min) of lunch increased by 23.7%, while AUC of C-peptide decreased by 42.5% after lunch. However, basal value of C-peptide was 3.7 ng/mL and 1.8 ng/mL, with breakfast and without breakfast, respectively. Consequently, it seems to be rather difficult to compare the both and to speculate the detail.

In other study, T2DM patients were investigated with 2 kinds of breakfast provided [29]. One is carbo-breakfast with PFC=15:20:65%, another is protein-breakfast with PFC=35:20:45%. When lunch including 65% of carbohydrate was given to both groups, protein-group showed higher insulin and C-peptide response, with lower postprandial hyperglycemia. Insulin, C-peptide and GIP levels showed the second-meal phenomenon, keeping the glucose concentrations controlled.

There was also an experiment for glucose increase in four conditions on ingestion of carbohydrate 50 g [30]. These protocols are as follows: only rice, salad + rice, rice + yogurt, and yogurt + rice, respectively. The result for the increment of blood glucose on 30 minute was 39.0 mg/dL, 19.4 mg/dL, 29.2 mg/dL, 15.9 mg/dL, respectively. The latter three group revealed reduced postprandial hyperglycemia compared with only rice group. These results would suggest the effect of taking salad and/or yogurt together for decreasing the risk of high glucose.

Furthermore, some reports were found with mixed meal challenge on breakfast. T2DM patients were provided 3 kinds of breakfast, which are 1) WB: whey diet 28 g with 42 g total protein, 2) PB diet: various protein 42 g, 3) CB: high-carbo with 17 g protein [31]. Overall postprandial AUC glucose was reduced by 12% in PB diet and by 19% in WB diet, compared with CB diet. Increment of C-peptide would be 7.4, 4.0, 1.0 pg/mL, respectively. After 12 weeks, decrease of HbA1c and body weight were, 0.89%, 0.6%, 0.36%, and 7.6kg, 6.1 kg, 3.5

kg, respectively. Thus, whey protein-based breakfast could become an important adjuvant for T2DM.

Responses of glucose, insulin, C-peptide and Triglyceride were investigated between Red Meat/Refined Grain Diet and Dairy/Chicken/Nuts/Whole Grain Diet [32]. In each group, carbohydrate amount per day and CP-incremental AUC were 218 g vs 181 g, 8.6 vs 6.4 nmol/L/3 h ($p<0.002$), respectively. Compared the results from insulin and c-peptide data, insulin sensitivity and hepatic insulin clearance would be involved.

In response to a mixed meal challenge, GLP-1-induced insulin secretion was found [33]. It was significantly reduced in people with impaired glucose tolerance, compared with those with normal glucose tolerance.

After mixed nutrient preload, glucose tolerance was relieved in proportion to the degree of T2DM [34]. Investigating responses to nutrient ingestion might reveal pathophysiological mechanism of T2DM, leading to a potent tool to improve glycemic control.

As mentioned above, researches on breakfast containing complex nutrients are progressing. Since the content is not single nutrient, these studies would have limits and problems to be solved. They may include various kinds of mixture for nutrients in the meal, different speed of digestion and absorption for each subjects, and response ability of insulin and C-peptide secretion. However, our current research concerning CPI-Carbo70 might become a reference data for future diabetic practice and research.

Conclusion

In current study, we investigated the response of blood glucose and C-peptide for carbohydrate 70 g and proposed the usefulness of CPI-Carb70. This index could become one of the simple and useful tool for evaluating pancreas function and glucose variability. This report would provide one of the basal data in the clinical practice and research development.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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