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Research Article

Index of C-peptide / glucose ratio for Carbo70 can be useful in clinical practice for diabetes

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Abstract

Background: Authors and colleagues have undertaken clinical research on Carbohydrate (CR) and Low Carbohydrate Diet (LCD) for years. We have proposed new evaluation method of insulinogenic index-carbohydrate 70g (IGI-carbo70). In similar way, C-peptide index for Carbohydrate-70 (CPI-Carbo70) is proposed in this report.

Subjects and methods: The subjects were 37 patients with Type 2 diabetes mellitus (T2DM) and admitted for further evaluation and treatment. CR diet was provided on day 1 and 2, including 60% carbohydrates, 25% lipids and 15% protein with 1400 kcal/day. On day 2, breakfast with 70g of carbohydrate was provided, and glucose and C-peptide values were measured at 0 and 30 minutes.

Results: Average HbA1c was 8.1 %, and Morbus (M) value was 70.5 in median. Glucose and C-peptide on 0--30min significantly increased as 163--195 mg/dL, 1.1--1.5μU/mL, respectively. CPI-Carbo70 was 1.94 in average and 1.54 in median. There were significant correlations between increments of glucose and C-peptide, and between HbA1c and CPI-Carbo70.

Discussion and conclusion: CPI-Carbo70 was investigated and proposed. It may be useful for evaluating the function of the pancreas. This research would give the fundamental data for this field, and further research development will be expected in the future.

Abbreviations: CPI-Carbo70: C-peptide index for Carbohydrate-70, IGI Insulinogenic index, Carbo70: Carbohydarate 70g, CR: Calorie Restriction, LCD: low carbohydrate diet, T2DM: type 2 diabetes mellitus, M value: Morbus value, MAGE: mean amplitude of glycemic excursions, IRI: immunoreactive insulin, 75gOGTT: 75g oral glucose tolerance test.

Introduction

Diabetes has been a medical and social serious problem in the world. Its number of diabetic patients is increasing and about 425 million, including 30 million in United States, 73 million in India and 110 million in China [1]. The cause related to this situation include various factors such as endocrine / metabolic impairment, obesity, changing meal and lifestyle with aging [2].

Then, there have been various comments concerning diabetes guidelines. Recently, the American College of Physicians (ACP) presented official comments concerning diabetes [3]. Among them, rather surprising statement was found that clinicians should set the management goal for HbA1c in most type 2 diabetic patients to be 7% or more and less than 8%. It has made a paradigm change for diabetic treatment.

On contrast, American Diabetes Association (ADA) released comments about goals and treatment for diabetes associated with complications of cardiovascular disease and the prevention of recurrence in the treatment for diabetes [4].

As to nutrition therapy for diabetes, there are continuing discussion concerning Calorie Restriction (CR) and Low Carbohydrate Diet (LCD) for years [5-8]. Atkins and Bernstein originally have begun to introduce LCD [9,10]. After that, clinical predominance of LCD has been gradually known and more prevalent in European and North-American region. On contrast in Japan, authors and colleagues have started LCD, and reported thousands of cases with clinical efficacy [11,12]. Moreover, we have investigated related research concerning LCD formula meals, elevated ketone bodies, Morbus (M) value, lipid metabolism and renal function [13-15].

We have undertaken clinical research on CR and LCD meals in a series of studies. Among them, a breakfast containing 70 g of carbohydrate was administered instead of 75 g of glucose, and the reaction of blood glucose and insulin (immunoreactivity insulin, IRI) was studied. As a result, insulinogenic index (IGI) for Carbo 70 was reported on insulin response to Carbo 70 [16].

Along the similar method of clinical research for Carbo70, we have studied the responses of blood glucose and C-peptide to Carbo 70 and describe in this paper.

Subjects and methods

The subjects who were enrolled in this study were 37 patients (M/F 15/22) with Type 2 diabetes mellitus (T2DM). Their ages were 35-80 years old, with 62.5 years old in average. Diabetic subjects were admitted for 14 days for further evaluation and treatment of T2DM. They were on the protocol of diet therapy as in-patients.

Methods included in the following steps. 1) Calorie Restriction (CR) diet was given for the subjects on day 1 and 2. CR had 60% carbohydrates, 25% lipids and 15% protein with 1400 kcal/day. 2) Low Carbohydrate Diet (LCD) was given from 3 to 14 days, which had 12% carbohydrates, 64% lipids and 24% protein with 1400 kcal/day. This meal of LCD has been so-called "super-LCD formula" in our research for years, which is one of the Very low-carbohydrate ketogenic diet (VLCKD) by the definitions of LCD [17-19].

Thus, both protocol with CR and LCD was continued for years in our clinical research. However, in current study, we have used only the breakfast on day 2. CR meal includes 840kcal of carbohydrate per day, which equals totally 210g of carbohydrate in 3 meals, according to the nutrients balance of PFC (protein, fat, carbohydrate) from the guideline of Japan Diabetes Society [20]. Then, breakfast including 70g of carbohydrate was provided to the patients after overnight fasting.

The detail of the examination is as follows: 1) basal biomarkers were measured in fasting on day 2, 2) blood glucose and C-peptide value were measured before breakfast (0 min), 3) patients has taken breakfast with 70g of carbohydrate, 4) glucose and C-peptide were measured 30 minutes after breakfast, 5) values of 0 min, 30 min and increment of glucose and C-peptide were measured, 6) index of ratio for increment of C-peptide / glucose which is CPI-Carbo70 was calculated and analyzed.

Daily glucose profile and Morbus value

As to daily glucose profile on day 2, we measured blood glucose 7 times a day, which are 8, 10, 12, 14, 17, 19, 22h. From these data, 2 biomarkers were calculated, which are average glucose level and M value.

M value has been known as the one of the useful index indicating both blood sugar level and mean amplitude of glycemic excursions (MAGE) [21-23]. When investigating glucose variability, daily profiles of blood glucose was measured, and average glucose level and M value can be calculated. M value has been formerly proposed for researching the status of MAGE. This index has been calculated as a logarithmic transformation of the deviation of glycemia from an arbitrary assigned "ideal" glucose value. It can express both the mean glucose value and the effect of glucose swings [21-24].

The formula of M value is defined as follows: $M = M^{BS} + M^{W}$, where $M^{W} = $ (maximum blood glucose – minimum glucose)/20; M^{BS} = the mean of MBSBS; MBSBS = individual M-value for each blood glucose value calculated as (absolute value of $[10 \times \log$ (blood glucose value/120)$])^3$. It can be understood by the equation [21-24].

In the case of interpretation of M value, the standard range has been <180, with borderline 180-320 and abnormal >320. Formerly, ideal sampling times a day has been in discussion. Through several experimental research, it had showed similar results on 7 times or 20 times per day [21-23,25]. It also showed similar result in comparison with continuous glucose monitoring (CGM) [23,25,26].

Statistical analyses

Obtained data in current study were represented as the mean +/- standard deviation (SD) and also represented median, quartile of 25% and 75% in the results of biomarkers. For performing statistical analyses, correlation coefficients were calculated by using Spearman test of the Microsoft Excel analytical tool widely used, which is Four steps Excel Statistics 4th edition [27].

Ethical considerations

Present study 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). Moreover, we have established an ethical committee including doctor, nurse, pharmacist and expert in the medical/legal specialty. We have discussed and made confirmation that this study is valid and agreed with all members without any problems. Furthermore, informed consents and written paper agreements have been obtained from the subjects. The study was registered with UMIN #R000031211.

Results

1) Basal data

This study enrolled 37 patients of T2DM. Their basal data were summarized in Table 1. Values are expressed by average and standard deviation, and also by median [25% - 75%]. The average age was 62.5 years old, with 65 years old in median. Data of HbA1c was 8.1 % in average and 7.7% in median. M value calculated from the daily profile of glucose on day 2 was 70.5 [43.2 – 203] (median [25 % - 75 %]).

2) Carbohydrate loading

Table 1. Subjects and basal data

		mean ± SD	median [25% - 75%]
Subjects			
	number of cases	37	37
	sex (male/female)	15/22	15/22
	age (years old)	62.5 ± 10.9	65 [55 - 68]
Glucose profile			
	HbA1c (%)	8.1 ± 1.8	7.7 [7.0 - 9.2]
	average glucose (mg/dL)	203.7 ± 71.2	187 [161 - 228]
	Morbus value	186.5 ± 256.1	70.5 [43.2 - 203]

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

		mean ± SD	median [25% - 75%]
Response of blood glucose			
	glucose- 0 min (mg/dL)	162.5 ± 54.9	142 [134 - 186]
	glucose-30 min (mg/dL)	194.7 ± 65.2	186 [155 - 214]
	increment (⊿) (mg/dL)	32.2 ± 26.4	22 [13 - 46]
Response of C-peptide			
	C-peptide- 0 min (ng/mL)	1.08 ± 0.65	0.9 [0.7 - 1.4]
	C-peptide-30 min (ng/mL)	1.52 ± 0.83	1.4 [1.0 - 1.9]
	increment (⊿) (ng/mL)	0.44 ± 0.41	0.4 [0.2 - 0.5]
Index of C-peptide for carbo-70			
	⊿CPR/⊿BG	1.94 ± 1.51	1.54 [0.83 - 2.5]

Changes in biomarkers data in response to 70g of carbohydrate intake were shown in Table 2. The values included blood glucose and C-peptide in 0 and 30 min. Data are expressed by the average, standard deviation, median and quartile of 25% and 75%.

3) Correlation among HbA1c, glucose and M value

Mutual correlations among HbA1c, average blood glucose and M value were investigated. Average blood glucose and M value were calculated from 7 points of daily blood glucose levels. There was significant correlation between average glucose and HbA1c ($p<0.01$) (Figure 1). Similarly, there was significant correlation between average blood glucose and M value ($p<0.01$) (Figure 2).

4) Correlation among HbA1c, glucose and M value

Correlation of increments of glucose and C-peptide for Carbo70 is shown in Figure 3. Both factors revealed significant correlation ($p<0.01$). There was significant negative correlation between HbA1c value and CPI-Carbo70 (Figure 4).

Discussion

We have been investigating research concerning M value in CR and LCD and related clinical studies. In this study, significant correlation was found between HbA1c and mean blood glucose, and between mean blood glucose and M value. This result would indicate the adequate validity of evaluation method using these three biomarkers.

The response of insulin and C-peptide to GTT and insulinogenic index (IGI) studies are found to evaluate the function of the pancreas in
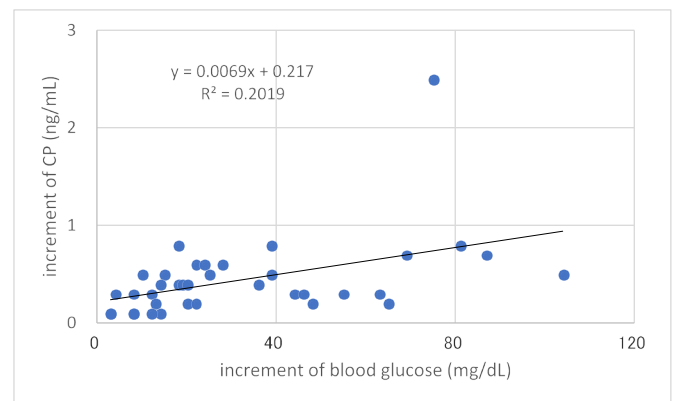

Figure 1. Correlation between average blood glucose and HbA1c.
There was significant correlation between them ($p<0.01$).

Figure 2. Correlation between Morbus value and average blood glucose.
There was significant correlation between them ($p<0.01$).

Figure 3. Correlation between increment of blood glucose and increment of CP
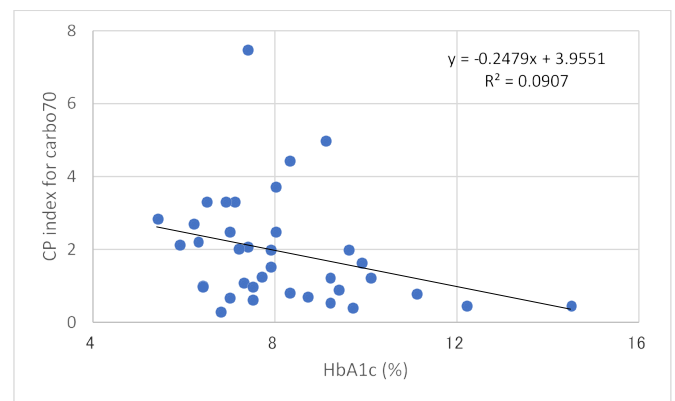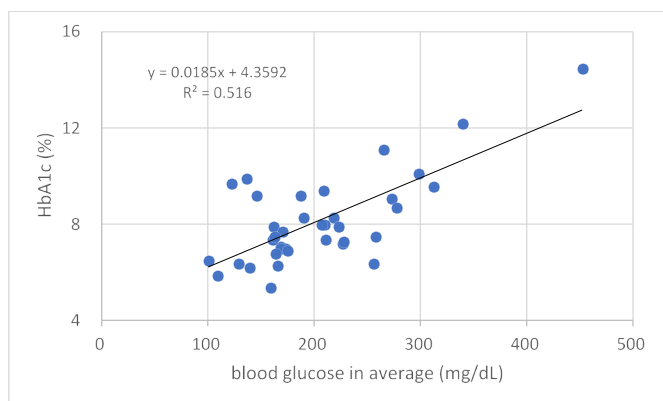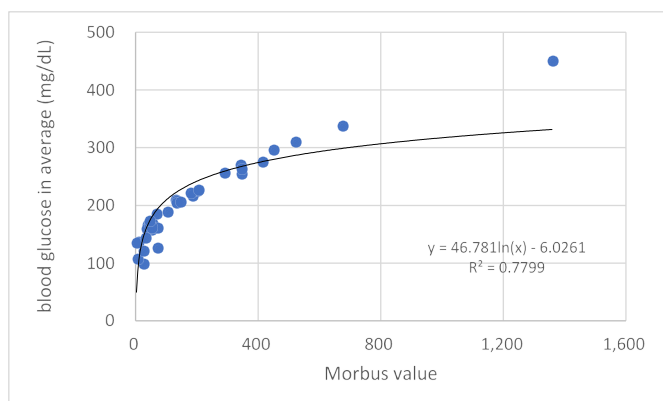Significant correlation was observed between them ($p < 0.01$).

Figure 4. Correlation between HbA1c and CP index for carbo70
Significant correlation was observed between them ($p < 0.05$).

diabetes [28]. Peak C-peptide for GTT seems to be at 30 min in healthy young and 60 min in healthy elderly [29]. All non-diabetic control subjects showed a peak of at least 6.5 ng/ml and an increment of at least 4 ng/ml. Ratio of C-peptide increment / glucose increment at 0-30 min. was inversely related to the prevailing fasting blood glucose (FBG) [29].

In clinical practice for diabetes, Insulinogenic index (IGI) has been one of the simple and useful marker calculating the ratio of insulin increment to glucose increment in 75g OGTT at 30min [30]. Recent study revealed that the average IGI was 1.00, 0.69 and 0.46 in 3 groups, including normal glucose tolerance (NGT), group with fasting glucose 100-109 mg/dL, group with fasting glucose 110-125 mg/dL, respectively [31]. In the case of T2DM with and without aggravation of parameters, IGI in average was showed 0.3 and 0.5, respectively [32].

There is a famous fast food named Gyudon, which is a rice bowl topped with beef. Glucose response to eating Gyudon was studied. It has protein 18.4g, fat 20.9g and carbohydrate 82.9g, which was given to 12 healthy volunteers with 26.9 years old in average [33]. Blood glucose increased 65 mg/dL at 30min in average. Thus, even if the subjects are healthy, blood glucose increase seems to be remarkable for taking 82.9g of carbohydrate.

In this analysis, there was a significant correlation between rise in blood sugar for Carbo 70 and rise in C-peptide, and a significant correlation was also found between HbA1c value and CPI-Carbo70. From this result and other previous related papers, it seems to be useful to investigate insulin response and pancreatic function by the load of Carbo 70 instead of 75 g glucose.

This research would have some limit as follows; 1) both response of IRI and C-peptide were not measured simultaneously, 2) meal includes not only carbohydrate but also protein and lipids, which may influence the response of glucose and c-peptide, 3) the function of ingestion and absorption would also influence the response.

Conclusion

In this report, the response of C-peptide and CPI-Carbo70 were described and proposed. As an alternative examination for 75 g OGTT, CPI-Carbo70 may be simple and useful for evaluating the function of the pancreas. This research would give the fundamental data for this field, and further research development will be expected in the future.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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