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Investigation of Fasting Ratio of C-Peptide/Glucose and Related Markers in Diabetes

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Abstract

***Background:** Authors have continued research concerning Low Carbohydrate Diet (LCD) and its related biomarkers. We also investigated correlation among several factors such as daily profile, fasting and average of blood glucose, Morbus value, and insulin and C-peptide.*

***Subjects and Methods:** Subjects were patients with type 2 diabetes mellitus (T2DM), classified into three groups due to HbA1c value. Methods included 1) basal blood exams, 2) intake of Calorie Restriction (CR) meal with 1400kcal/day with 60% of carbohydrates, 3) check of daily blood glucose 7 times a day, 4) calculation of average glucose and M value, 5) analyses of biomarkers.*

***Results:** Average blood glucose was 168 mg/dL, 206 mg/dL, 265mg/dL in low, middle, high group, respectively. Fasting ratio of C-peptide/glucose in 3 groups was 0.37, 0.34, 0.26, respectively period. There was significant correlation among HbA1c, M value and fasting ratio of C-peptide/glucose.*

***Discussion and Conclusion:** Among 3 groups, high group revealed lower tendency of fasting C-peptide and fasting ratio of C-peptide/glucose than other groups, suggesting that high group might has lower ability of insulin secretion. Fasting ratio of C-peptide/glucose would be useful for indicating beta cell function and predicting insulin requirement in clinical practice.*

Keywords: *Fasting ratio of C-peptide/glucose; Calorie Restriction (CR); C-peptide (CP); type 2 diabetes mellitus (T2DM); C-peptide index (CPI).*

Abbreviation

CR: Calorie Restriction

LCD: low carbohydrate diet

T2DM: type 2 diabetes mellitus

M value: Morbus value

MAGE: mean amplitude of glycemic excursions

75gOGTT: 75g oral glucose tolerance test

MTT: meal tolerance test

CPI: C-peptide index

Introduction

In recent decades, there have been various nutrition and metabolic problems in developing and developed countries. Metabolic syndrome (Met-S) such as obesity and diabetes has increased, which was formerly called syndrome X. [1]. It has become inevitable medical and social issues to be resolved [2, 3]. There are lots of factors to be influenced by country, meal habit, lifestyle, age, exercise, economic situation, and so on. Diabetes has been increasing rapidly in the world. It

has a variety of complications with macro- and micro-angiopathy including large vessels of head, heart, leg and neuropathy, retinopathy and neuropahy [4]. Consequently, several guidelines for treating diabetes has been presented for better management in the countries [5, 6]. International Diabetes Federation (IDF) proposed the Standards of Medical Care, in which evaluating the intake and counting amount for carbohydrate with experience-based calculation would be emphasized [7]. Recent discussion has been focused in the recommended HbA1c level in various situations, especially between American Diabetes Association (ADA) and American College of Physicians (ACP) [8, 9].

On the other hand, we have observed the continuing discussion about the ideal nutrition treatment for diabetes. They include the comparison between Low Carbohydrate Diet (LCD) and Calorie restriction (CR) diet by many researchers. LCD was begun by Bernstein and others, which was wide spread after that in western countries [10]. Consecutively, there were lots of reports for beneficial effects of LCD compared with CR [11-13].

In Japan, author and colleagues have started and continued clinical research concerning LCD [14]. We proposed actually simple and useful LCD formula including super, standard and petit LCD, which can be applicable to every occasion [15]. Moreover, we have investigated some reports in relation to hypercholesterolemia, renal function, ketone bodies and actually simple and useful LCD formula including super, standard and petit LCD [16-18]. Furthermore, we have developed social movement through the activity of Japan Low Carbohydrate Diet Promotion Association.

As mentioned above, we have continued clinical research about diabetes, CR and LCD. Our research protocol has breakfast of CR with 70g of carbohydrate. Through our research program, we have proposed breakfast similar to 75 g of glucose tolerance test. Pancreatic function can be speculated by the response of insulin and blood glucose [19]. In order to develop this research, we investigated fasting ratio of C-peptide and blood glucose, as well as fasting and average blood glucose and Morbus (M) value calculated for a day in this study.

Subjects and Methods

In current study, we enrolled patients with type 2 diabetes mellitus (T2DM). They were admitted for further evaluation and treatment for T2DM. According to the value of HbA1c, they were classified into three groups which was low, middle, high, respectively. The account number of the cases in each group was 15, 15, 16, respectively.

Methods are from our usual procotol for diabetic investigation. It includes providing Calorie Restriction (CR) diet on Day 1 and 2, and changing into Low Carbohydrate Diet (LCD) after day 3.

In current study, a series of procedure was as follows: 1) On the morning of Day 2, we have measured basal biomarkers concerning diabetes after overnight fast, including blood glucose and C-peptide (CP). Blood samples were drawn before breakfast, after the patient was keeping still more than 15 minutes. 2) After taking blood samples, breakfast was given to the subjects, which was includes protein PFC ratio (protein 15%, fat 25%, carbohydrate 60%) with 1400 kcal/day. As to breakfast, carbohydrate amount is 70g. This is along to the standard nutrition guideline in Japan, proposed from Japan Diabetes Society (JDS) [20].

Formula of C-Peptide and M Value

The formula of Fasting ratio of C-peptide/glucose is defined as 100 x fasting C-peptide value / fasting glucose. Blood sample was obtained on the morning of Day 2 after overnight fast.

As to the glucose variability, we checked the daily profile of blood glucose on day 2 for7 times a day. The time was 0800, 1000, 1200, 1400, 1700, 1900, 2200h. According to these data, average blood glucose in a day on Day 2 and also M value were calculated.

M value is one of the biomarker which indicates average blood glucose level and also the mean amplitude of glycemic excursions (MAGE)[21,22]. M value can indicate average and swinging degree of blood glucose. It can be calculated for a logarithmic transformation of the deviation of glucose from ideal glucose value[21-23].

Detail of M value is in the following. At first, $M = M^{BS} + M^{W}$: M value is the total of M^{BS} and M^{W}. Secondly, M^{W} is maximum blood glucose − minimum glucose)/20. Thirdly, M^{BS} is the mean of MBSBS. Finally, MBSBS is the individual M-value for each blood glucose,

calculated as (absolute value of [10 × log (blood glucose level/120)])^3 [20-22].

The evaluation for the M value reveals that normal is less than 180, borderline is from 180 to 320, abnormal level is more than 320. From the experimental research, there are similar results in the case of sampling of 7 times or 20 times a day. Furthermore, obtained data would be compatible with that of continuous glucose monitoring (CGM) [22-24].

Statistical Analysis

In current study, data were represented by the median and quartile of 25% and 75% according to the biomarkers. It is described as median [25% – 75%]. Statistical investigation involved the usage of correlation coefficients, according to the Spearman test. The reference method was used on the analytical evaluation [25].

Ethical Standard

This research was conducted in compliance with the ethical principles based upon the Declaration of Helsinki. Moreover, additional commentary was done in 2004 General Assembly Tokyo, Japan. It was 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. There was also "Ethical Guidelines for Epidemiology Research" by the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare.

Authors had an ethical committee that includes doctor, nurse, pharmacist and expert in the legal specialty. We have discussed and confirmed that current study is valid and agreed with all members. In addition, informed consents and written paper agreements have been obtained from the subjects. This investigation has been registered in the open database (UMIN) by National University Hospital Council of Japan (ID: #R000031211).

Results

Fundamental Data

There were fundamental data in three groups, which were revealed in Table 1. Among these, there are similar ages in 3 groups, and the median HbA1c was 6.8%, 7.9%, 9.7%, respectively. Average blood glucose and M value showed increasing level in the order of group 1 to 3, in which the difference of numerical value is larger in M value than that in glucose.

Fasting Glucose

Fasting level of blood glucose in 3 groups are shown in Fig.1. In the 3 groups, median value was 138mg/dL, 157mg/dL, 146mg/dL, respectively, which was not increased in low, middle, high group (Fig.1). On contrast, average value was 168 mg/dL, 206 mg/dL, 265mg/dL, respectively, which was increased in the order of group 1 to 3 (Table 1).

Table 1. *Subjects and basal data*

	Group 1	Group 2	Group 3
Subjects age(median [25% - 75%] age(min-max) count(number)	 37 [60 - 68.5] [35 - 75] 15	 62 [52 - 71.5] [47 - 79] 15	 65 [61 - 68.5] [41 - 80] 16
Glucose profile HbA 1 c (%) average glucose (mg/dl) Morbus value	 6.8 [6.4 - 7.1] 168 [149 - 174] 51 [40 - 61]	 7.9 [7.6 - 8.0] 206 [166 - 214] 130 [62 - 156]	 9.7 [9.2 - 10.0] 265 [177 - 282] 326 [57 - 422]

Fasting C-peptide

Fasting value of C-peptide in 3 groups are shown in Fig.2. In the 3 groups, median value was 0.9ng/mL, 0.9ng/mL, 0.75ng/mL, respectively. There are similar value between group 1 and 2.

Fasting Ratio of C-Peptide/Glucose

The data of the fasting ratio of C-peptide/glucose in 3 groups are shown in Fig.3. The value was in 3 groups was 0.37, 0.34, 0.26, respectively, which is decreasing in the order of group 1 to 3. This ratio is involved in glucose (Fig.1) and C-peptide (Fig.2).

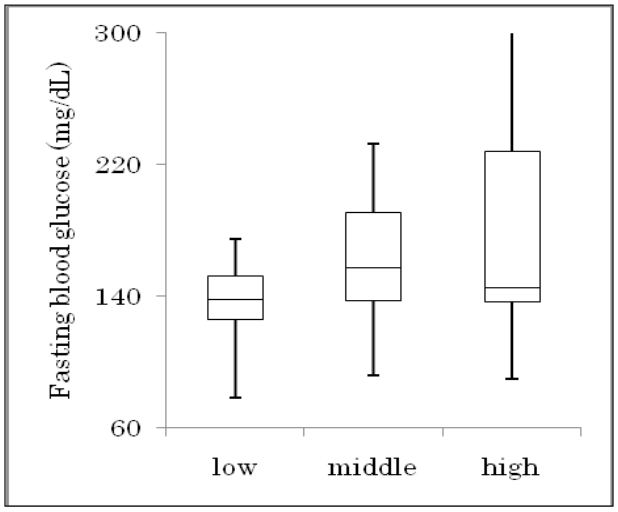

Figure 1. *Fasting level of blood glucose in 3 groups*

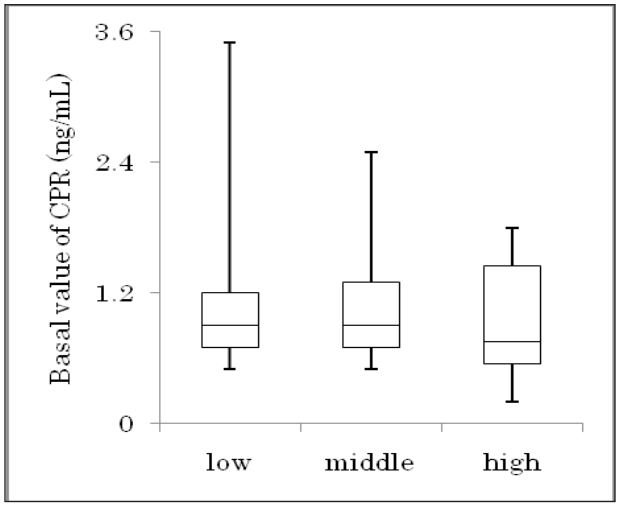

Figure 2. *Fasting value of C-peptide in 3 groups.*

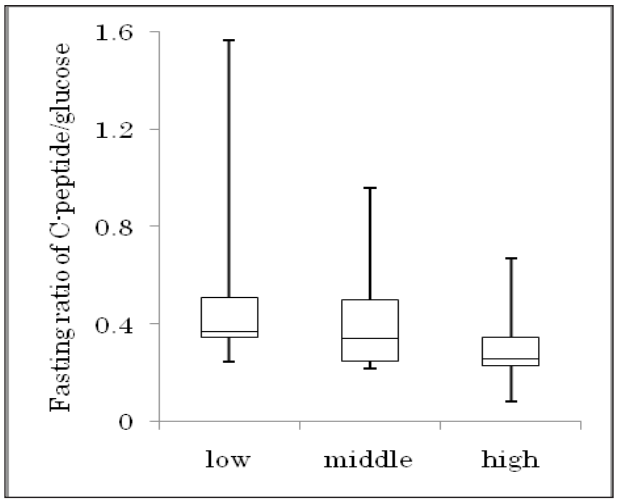

Figure 3. *Fasting ratio of C-peptide/glucose in 3 groups*

Correlation among HbA1c, M Value and Ratio of CP/Glucose

There was significant negative correlation between HbA1c and fasting ratio of CP/glucose ($p<0.05$) (Fig.4). Similarly, there was significant negative correlation between M value and fasting ratio of CP/glucose ($p<0.05$) (Fig.5). On contrast, there was not significant correlation between average blood glucose and fasting ratio of CP/glucose (Fig.6).

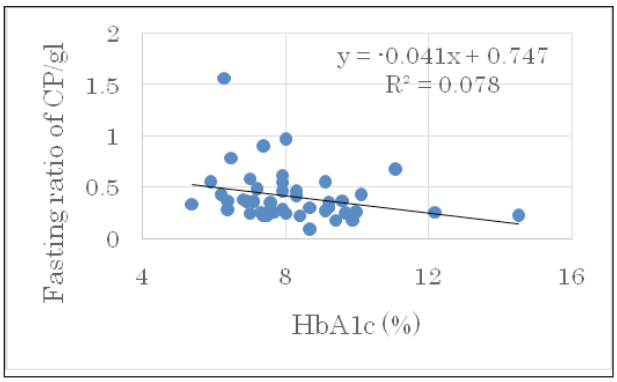

Figure 4. *Correlation between HbA1c and Fasting ratio of CP/glucose*

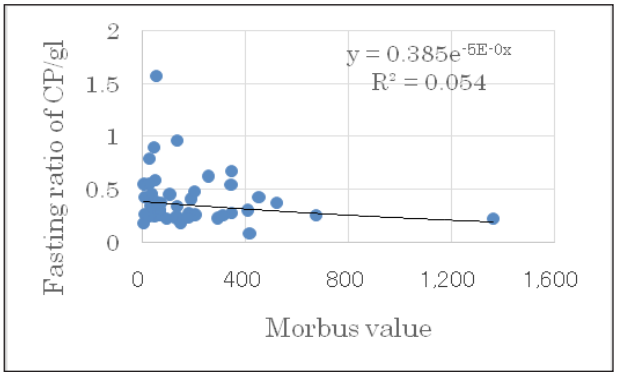

Figure 5. *Correlation between M value and Fasting ratio of CP/glucose*

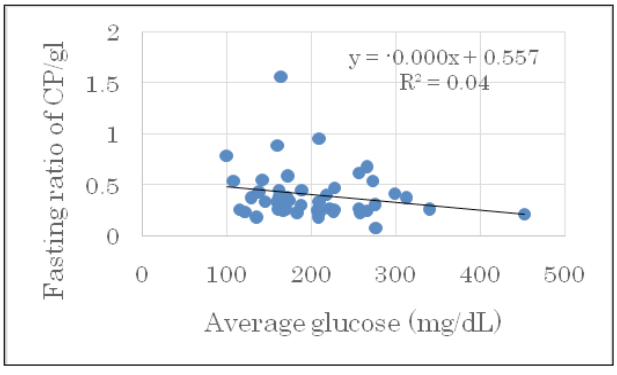

Figure 6. *Correlation between Average glucose and Fasting ratio of CP/glucose*

Discussion

Research on CR and LCD on diabetes diet therapy has advanced in the world with the accumulation of lots of evidence. In this field, authors have been continuing our research in two axes.

The first axis is a comparison between two types of meals, CR and LCD. Blood glucose profile, mean blood glucose level, blood glucose fluctuation, urinary CP excretion are different between both groups [26]. Furthermore, the M value indicating both the mean blood glucose and the blood glucose fluctuation has been useful for clinical research [27].

As the second axis, we examined the variation of blood glucose, insulin and C-peptide for breakfast intake containing a certain amount of carbohydrate [19]. Conventionally, 75g oral glucose tolerance test (75g OGTT) has been performed to examine the function of the pancreas [28]. This is definitely meaningful, but its adaptation has declined in recent years.

As a substitute, studies by the meal tolerance test (MTT) are also performed in the clinical setting [29, 30]. MTT has been usually provided as breakfast. One of the standard MTT has 450 kcal including 15% protein, 35% fat, 50% carbohydrate, 1.6g salt [29, 30]. In this case, carbohydrate amount is calculated to be 56g per breakfast.

This report is a joint study of the above two axes. As to the subjects, the background of 3 groups was almost equivalent, and the difference of M value was larger than that of HbA1c. M value represents both average blood glucose level and mean amplitude of glycemic excursions (MAGE) [23, 24, 27]. The obtained numerical level of M value has always larger differences compared with that of HbA1c. Then, it seems to be useful as clinical research, for tracking one person and also for comparison with many cases.

Regarding our current data, fasting blood glucose in median showed similar levels in 3 groups (low, middle, high), and the data was rather scattered widely in high group. High group revealed lower tendency of fasting C-peptide and fasting ratio of CP/Glucose than other two groups. These results suggest that high group might has lower secretion of insulin, while low and middle group might include inhomogeneous cases with various pancreatic function.

For the correlation with fasting ratio of C-peptide/glucose, R^2 value was 0.078, 0.054, 0.040 in HbA1c, M value, average blood glucose respectively. The former two showed significant correlation ($p < 0.05$), and further evaluation would be necessary and expected for accumulation of cases in the future study.

As for the terminology of Fasting ratio of C-peptide/glucose, there was formerly the C-peptide index (CPI) which has the same meaning. However, CPI might show misunderstanding of the index, because there were several research concerning C-peptide/glucose on 0min, 30min, 120min and delta (incremental) value between 0-30min, as well as the index of multiplying Fasting C-peptide and fasting glucose [31, 32]. From these situation, Fasting ratio of C-peptide/Glucose will be used in this report.

There was a report that postprandial serum C-peptide to plasma glucose concentration ratio would be used for index of β-cell function [32]. Interestingly, there is a novel index using fasting C-peptide and fasting glucose values [33]. It is defined as Fasting C-peptide x fasting glucose /20 would be a simple and would be an effective index of insulin resistance better than HOMA-IR in Japanese patients with T2DM [33].

Predictors of the future insulin use were investigated among fasting ratio of C-peptide/glucose, body mass index, fasting glucose, C-peptide level [34]. As a result, these factors were strong predictors of future insulin use in T2DM. According to the results of fasting ratio of C-peptide /glucose, there were divided into 3 groups, which were 1.7, 1.0, 0.4 in group 1,2,3, respectively. The percentage of the patients with insulin treatment was 8%, 24%, 46%, respectively [34]. Thus, fasting ratio of C-peptide/glucose would be useful for speculation of decreasing pancreas function and inducing insulin therapy in the future.

There is another clinical study for pediatric patients with T2DM [35]. The ratio of mean blood glucose / fasting blood glucose may represent beta cell function rather than HbA1c and fructosamine. Its median value was 1.48 with HbA1c 7.9%, while our value in this study is 1.24 with HbA1c 7.9%. Possible reason of the difference might be from age, secretion ability and resistance of insulin.

Another research showed the usefulness of fasting ratio of C-peptide/glucose. For clinical diagnosis of type 1 and 2 diabetes or for insulin treatment, three

indexes would be used for judgement [36]. They are fasting C-peptide, fasting ratio of C-peptide/glucose and HOMA-ßC-peptide-index. Thus, fasting ratio of C-peptide/glucose could be applicable clinical practice.

Conclusion

In summary, fasting ratio of C-peptide/glucose and related parameters were investigated in this study. The results suggest the clinical usefulness for predicting pancreatic function, and for beneficial application of diabetic clinical practice and research in the future.

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