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Proposal for Insulinogenic Index (IGI)-Carbo70 as Experimental Evaluation for Diabetes

Bando H[1]*, Ebe K[2], Muneta T[3], Bando M[4] and Yonei Y[5]

[1]Tokushima University/Medical Research, Tokushima, Japan
[2]Takao Hospital, Kyoto, Japan
[3]Muneta Maternity Clinic, Chiba, Japan
[4]Department of Nutrition and Metabolism, Institute of Biomedical Sciences, Tokushima University, Tokushima, Japan
[5]Anti-Aging Medical Research Center, Graduate School of Life and Medical Sciences, Doshisha University, Kyoto, Japan

Abstract

Background: The discussion has continued concerning Calorie Restriction (CR) and Low Carbohydrate Diet (LCD) for years. Authors and colleagues have continued clinical research on LCD. In this study, CR diet was given to diabetic patients and the new evaluation way of insulinogenic index-carbohydrate 70 g (IGI-carbo70) would be proposed.

Subjects and methods: The subjects were 48 patients with Type 2 diabetes mellitus (T2DM) and admitted for 14 days for further evaluation and treatment. CR diet was provided on day 1 and 2, including 60% carbohydrate, 25% lipids and 15% protein with 1400 kcal/day. On the morning of day 2, breakfast with 70 g of carbohydrate was given, and blood glucose and immune reactive insulin (IRI) at 0 and 30 min and IGI were investigated.

Results: Average HbA1c was 7.9% and Morbus (M) value was 108 in median. Glucose and IRI on 0-30 min significantly increased as 166-212 mg/dL, 4.3-1.9 μU/mL, respectively. Classified into 3 groups as to HbA1c level, low, middle and high group showed HbA1c 6.0%, 7.8%, 9.7%, respectively. Glucose and IRI on 0-30 min in median were 117-50, 166-203, 218-299 mg/dL, 4.4-12.8, 4.5-13.5, 4.2-9.9 μU/mL, with IGI 0.25, 0.14, 0.10, respectively.

Discussion and conclusion: Newly-proposed IGI-carbo70 was investigated, and there were several correlations among 8 related biomarkers. These findings suggest that current results would become the fundamental data and IGI-carbo70 could be the useful way to evaluate diabetic status by usual meal with mixed nutrients.

Keywords: (IGI-carbo70) Insulinogenic index-carbohydarate 70 g; (CR) Calorie restriction; (LCD) Low carbohydrate diet; (T2DM) Type 2 diabetes mellitus; (IRI) Immunoreactive insulin

Abbreviations: IGI-carbo70: Insulinogenic Index-Carbohydarate 70 g; 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; VLCKD: Very Low-Carbohydrate Ketogenic Diet; CGM: Continuous Glucose Monitoring; HOMA-R: Homeostasis Model Assessment-Insulin Resistance; HOMA-β: Homeostasis Model Assessment of β-cell Function; HDL-C: High density Lipoprotein Cholesterol; LDL-C: Low Density Lipoprotein Cholesterol; 75 g OGTT: 75 g Oral Glucose Tolerance Test

Introduction

The discussion has continued concerning Calorie Restriction (CR) and Low Carbohydrate Diet (LCD) for years [1-5]. Clinical predominance of LCD has been gradually known and more prevalent. In European and North American region, Atkins and Bernstein originally have begun to introduce LCD [6,7].

On contrast in Japan, the authors have started LCD, and reported thousands of cases with clinical efficacy [8,9]. Furthermore, we have investigated related research concerning 3 types of LCD formular meals, elevated ketone bodies, Morbus (M) value, lipid metabolism and renal function [10-12].

Through our clinical study, we always compared the differences of the glucose variability between CR and LCD. In this study, we have given CR diet to the patients with type 2 diabetes mellitus (T2DM), and investigated the responses of blood glucose, immunoreactive insulin (IRI) value and insulinogenic index (IGI), suggesting the usefulness of experimental application of IGI as an approach for clinical study.

Methods

The subjects enrolled in this study were 48 patients (M/F 23/25) with T2DM. They are 18-84 years old with 59.4 ± 12.9 (mean ± SD) years old in average, 60.5 years old in median value.

Subjects were admitted for 14 days for further evaluation and treatment of T2DM. The protocol of diet therapy was as follows: 1) Calorie Restriction (CR) diet was provided on days 1 and 2, which had 60% carbohydrate, 25% lipids and 15% protein with 1400 kcal/day. 2) Low Carbohydrate Diet (LCD) was provided from 3 to 14 days, which had 12% carbohydrates, 64% lipids and 24% protein with 1400 kcal/day. This LCD has been so-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 [12-14].

Methods included the measurements of responses for glucose and IRI against 70 g of carbohydrate on the morning of day 2. CR diet has 840 kcal of carbohydrate per day, which equals totally 210 g of

***Corresponding author:** Hiroshi Bando, Instructor, Tokushima University, Nakashowa 1-61, Tokushima 770-0943, Japan, Tel: +81-90-3187-2485; E-mail: pianomed@bronze.ocn.ne.jp

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carbohydrate in 3 meals. Then, breakfast including 70 g of carbohydrate was given to the patients after overnight fasting, with the measurement of blood glucose and IRI on 0 min and 30 min. Other blood biomarkers were measured in fasting on day 2.

The content of CR diet is along the guideline of Japan Diabetes Society, in which PFC ratio is 14.7%, 26.9%, 58.4%, respectively [15]. This ratio has been stable from 1985 to 2015 on the national survey in Japan [16].

Glucose profile and M value

On day 2, daily profile of blood glucose was studied 7 times a day, which are 8, 10, 12, 14, 17, 19, 22 h. According to the glucose level, 2 markers were calculated. One is the average glucose level, and another is Morbus (M) value. M value is a useful index representing both blood sugar level and mean amplitude of glycemic excursions (MAGE) [17-19]. As for the glucose variability, daily profiles of blood glucose were measured 7 times a day, and obtained data were calculated for average glucose level and Morbus (M) value. M value has been proposed for researching MAGE. This index has been calculated as a logarithmic transformation of the deviation of glycemia from an arbitrary assigned "ideal" glucose value, with an expression of both the mean glucose value and the effect of glucose swings [17-20].

$$\text{M - value} = \frac{\sum}{N} |\, M\frac{BS}{BS}\,| + W/20 \text{ where } M\frac{BS}{BS} = |\, 10\log\frac{PG}{120}\,|^3$$

M value is calculated by the formula 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×log (blood glucose value/120)])^3.

As to the interpretation of M value, the standard range is <180, borderline is 180-320 and abnormal is >320. Adequate sampling times a day have been argued for the detail and precise evaluation of glucose variability and MAGE. There were similar results on 7 times or 20 times of sampling per day [17-21] showing similar result in comparison with continuous glucose monitoring (CGM) [19-22].

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 [23].

Intergroup comparisons were made using the Wilcoxon rank sum test or the Bonferroni multiple comparison (Lambert method). A significance level of less than 5% obtained using a two-tailed test was considered to be statistically significant.

Ethical considerations

Current study was conducted in compliance with the ethical principles of the Declaration of Helsinki and 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). No ethical committee meeting was held. Informed consent was obtained from the subjects. The study was registered with UMIN #R000031211.

Results

Basal data

The basal data of 48 patients enrolled were shown in Table 1. The values are expressed by average, standard deviation and median (25%-75%). The average age was 59.4 years old, and average HbA1c was 7.9%. M value obtained from the daily profile of glucose on day 2 was 108 34.1-308 median 25%-75%.

Carbohydrate loading

Biomarkers data related to 70 g of carbohydrate intake were shown in Table 2. The values are expressed by the average, standard deviation, median and quartile of 25% and 75%. Responses of glucose and IRI against 70 g of carbohydrate were shown in Figure 1. Number of the subjects is 48. There was significant difference between glucose increase at 0 and 30 minutes, and between IRI increase at 0 and 30 minutes ($p<0.01$).

IGI-carbo70 in 3 groups

Glucose increase against carbohydrate 70 g was investigated in 3 groups (Figure 2). Subjects were classified into 3 groups according to HbA1c value. They are low, middle and high group, which HbA1c was 6.0 ± 0.5%, 7.8 ± 0.6%, 9.7 ± 0.9%, respectively. Each group has 16 subjects and showed significant glucose increase between 0 min and 30 min ($p<0.01$). In 3 groups, glucose on 0 min and 30 min in median were 117-150, 166-203, 218-299 mg/dL, respectively.

Table 1: Basal Data of Patient with T2DM.

	Mean ± SD	Median	25%-75%
Age (years old)	59.4 ± 12.9	60.5	54.5-68.3
HbA1c (%)	7.9 ± 1.7	8.1	6.4 - 8.9
Average Glucose (mg/dL)	196.3 ± 81.3	174.3	147-241
Morbus Value	207.3 ± 258	108	34.1-308
Triglyceride (mg/dL)	184.4 ± 239	101.5	70.8 -202
HDL-C (mg/dL)	66.8 ± 20.5	63.5	10.0-79.8
LDL-C (mg/dL)	140.4 ± 43.9	138.5	109-165
HOMA-R	2.0 ± 1.1	1.9	1.1-2.5
HOMA-β	21.6 ± 17.6	16.7	10.6-25.7

Table 2: Biomarker Related to Carbon-70.

	Mean ± SD	Median	25%-75%
Glucose 0 min (mg/dL)	169.1 ± 54.1	166	124-212
Glucose 30 min (mg/dL)	215.3 ± 64.1	212	160-269
IRI 0 min (μU/mL)	4.8 ± 2.2	4.3	3.0-6.2
IRI 30 min (μU/mL)	13.6 ± 9.8	11.9	7.8-18.0
Glucose Increase (mg/dL)	46.2 ± 25.5	36.5	29.0-63.5
IRI increase (μU/mL)	8.8 ± 8.7	7.3	3.5-10.8
IGI-Carbo70	0.28 ± 0.35	0.12	0.09-0.32

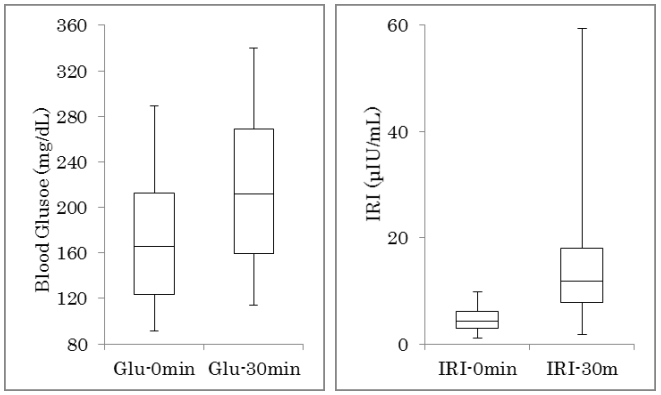

Figure 1: Responses of glucose and IRI against carbohydrate load of 70 g.

Similarly, IRI increase against carbohydrate 70 g was investigated in 3 groups (Figure 3). Each group has 16 subjects and showed significant IRI increase between 0 min and 30 min ($p<0.01$). IRI on 0 min and 30 min in median were 4.4-12.8, 4.5-13.5, 4.2-9.9 μU/mL, respectively.

Data from Figures 2 and 3, Insulinogenic Index (IGI)-carbohydrate 70 g (IGI-carbo70) was calculated and classified in 3 groups (Figure 4).

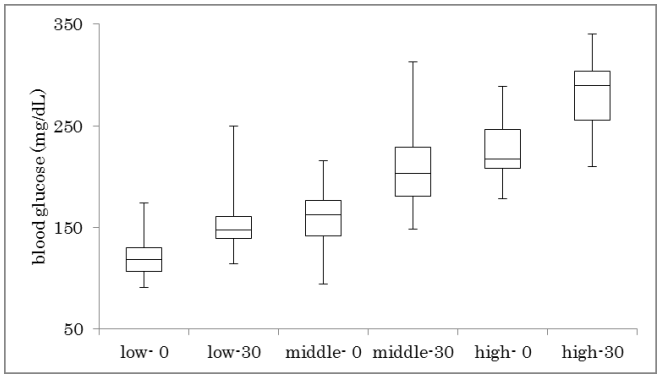

Figure 2: Glucose elevation against carbohydrate load of 70 g in 3 groups.

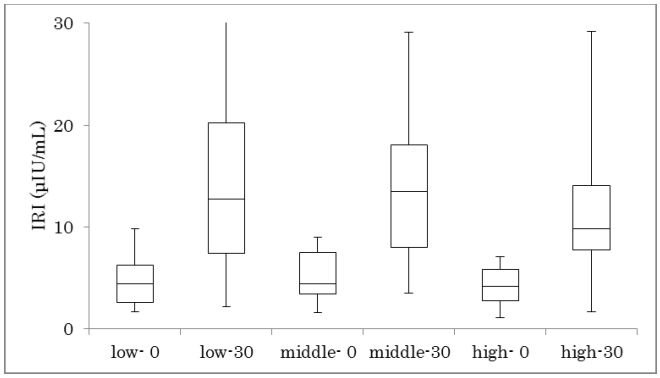

Figure 3: IRI elevation against carbohydrate load of 70 g in 3 groups.

The median level was decreased from low, medium and high group, with 0.25, 0.14 and 0.10, respectively.

Correlation of IGI-carbo70

Mutual correlations among IGI-carbo70 and other biomarkers were investigated (Table 3). IGI-carbo70 showed significant correlation with increment of glucose and IRI, and HOMA-β. M value showed significant correlation with basal glucose, increment of glucose and IRI, HOMA-R and HOMA-β.

Discussion

Insulinogenic index (IGI) has been useful marker which measures the ratio of insulin increment to glucose increment in 75 g OGTT at 30 min [24,25]. Recent study revealed that the average IGI was 1.00, 0.69 and 0.46 in 3 groups which were group of normal glucose tolerance (NGT), group with fasting glucose 100-109 mg/dL, group with fasting glucose 110-125 mg/dL [26]. Another study revealed that average IGI was 1.02 in 1265 normal young volunteers and 0.80 in 1076 obese

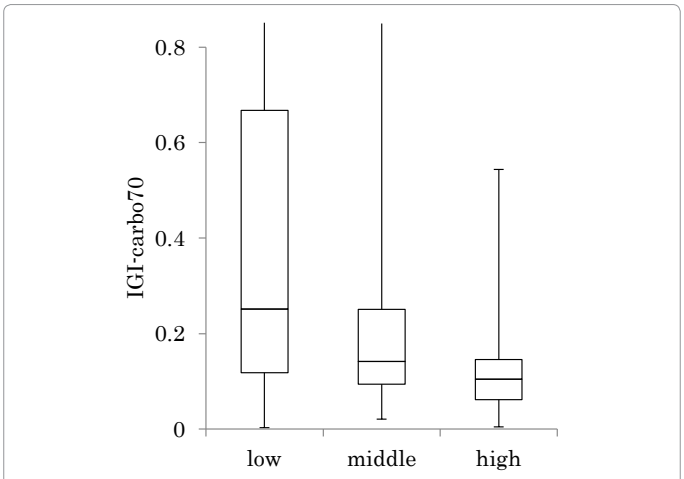

Figure 4: IGI-carbo70 in three groups.

Table 3: Correlation among 8 related factors.

	Basal		Increment		IGI-Carbo70	MorbusValue	HOMA		
	Glucose	IRI	Glucose	IRI			-R	-β	
Basal Glucose		-0.027	0.261	-0.13	-0.215	0.866	0.502	-0.755	C.C.
		0.854	0.067	0.365	0.132	<0.001	<0.001	<0.001	P.V.
Basal IRI	-0.027		-0.002	0.507	0.439	-0.117	0.849	0.59	
	0.854		0.989	<0.001	0.002	0.414	<0.001	<0.001	
Increment Glucose	0.261	-0.002		-0.014	-0.465	0.42	0.115	-0.123	
	0.067	0.989		0.924	0.001	0.003	0.431	0.398	
Increment IRI	-0.13	0.507	-0.014		0.852	-0.3	0.348	0.352	
	0.365	<0.001	0.924		<0.001	0.036	0.017	0.016	
IGI	-0.215	0.439	-0.465	0.852		-0.456	0.256	0.349	
	0.132	0.002	0.001	<0.001		0.001	0.079	0.017	
M value	0.866	-0.117	0.42	-0.3	-0.456		0.295	-0.734	
	<0.001	0.414	0.003	0.036	0.001		0.043	<0.001	
HOMA-R	0.502	0.849	0.115	0.348	0.256	0.295		0.132	
	<0.001	<0.001	0.431	0.017	0.079	0.043		0.367	
HOMA-β	-0.755	0.59	-0.123	0.352	0.349	-0.734	0.132		
	<0.001	<0.001	0.398	0.016	0.017	<0.001	0.367		

C.C: Correlation coefficient; P.V: P value; IGI-carbo70: Insulinogenic Index-carbo70; HOMA-R: Homeostasis Model Assessment Insulin Resistance; HOMA-β: Homeostasis Model Assessment for β Cell Function; IRI: Immuno-reactive Insulin.

Shadow areas represent significant correlations including <0.05, <0.01 and <0.001.

children/adolescents [27]. As to T2DM with and without aggravation of parameters, IGI in average was showed 0.3 and 0.5, respectively [28].

Furthermore, IGI has been used after a meal at 30 min [29-31]. The changes in IGI were correlated to the changes in the β-cell function in both normal glucose-tolerant and prediabetic individuals, which suggests it to be a valid proxy indicator for β-cell function in healthy individuals [29].

In Asian countries, overconsumption of starchy foods such as rice has induced a rapid and sharp postprandial hyperglycemia [32-34]. This increased glucose response is accompanied by an insulin surge and contributes to the etiology of diabetes [35].

Recently, effect of co-ingestion of amino acids with rice on glycemic and insulin response was investigated in 7 various patterns [36]. Rice with 68 mL of amino acid mixture showed the best results in reducing the peak blood level [36]. Its merit lies in enabling people living in Asia to reduce postprandial hyperglycemia due to carbohydrate-rich rice meals by the inclusion of a ready-to-drink amino acid mixture [37-39].

A liquid mixed meal test was tried for the indices of insulin secretion in patients with diabetes [40]. Participants ingested 237 mL high protein boost-HP (Nestle) consisting of 33 g carbohydrate, 15 g protein and 6 g fat, (%Calories: 55% carbohydrate, 25% protein, and 20% fat). IGI and also C-peptide-derived 30 minutes index and oral disposition index (ODI) from the mixed meal would be useful [41-43].

The effect of a rice bowl topped with beef to blood glucose was investigated [44]. This is one of famous Japanese fast food with protein 18.4 g, fat 20.9 g and carbohydrate 82.9 g, and it was given to 12 healthy volunteers with 26.9 years old in average. Blood glucose increased 65 mg/dL at 30 min. Thus, even if the subjects are healthy, blood glucose increase seems to be remarkable.

Ethnic difference for IGI was investigated using two 200 mL servings of Ensure Plus (Abbott Laboratories, Columbus, OH, USA) [45]. Each serving has 300 kcal, 40.4 g carbohydrate, 9.8 g fat and 12.5 g protein. Chinese, Malay and Asian Indians showed 36-45 mg/dL increase of blood glucose at 30 min, and its IGI was 0.64, 0.266 and 0.399, respectively.

Conclusion

Taking these results and discussion into consideration, research for postprandial hyperglycemia with mixed-nutrient load would be significant. Newly-proposed IGI-carbo70 was investigated, and there were several correlations among 8 related biomarkers. These findings suggest that current results would become the fundamental data and IGI-carbo70 could be the useful way to evaluate diabetic status by usual meal with mixed nutrients.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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