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A Trial of Analysis Method for Insulin Secretion Response to Carbohydrate Loading

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Abstract

Authors et al. have continued diabetic practice and research for long, and started Low Carbohydrate Diet (LCD) first in Japan. We developed social LCD movement by Japanese LCD Promotion Association (JLCDPA), and proposed petite-, standard-, super LCDs with carbohydrate 40%, 26%, 12%, respectively. Methods included 9 healthy medical staffs and two exams of 75g Oral Glucose Tolerance Test (OGTT) and Meal Tolerance Test (MTT). MTT means super-LCD breakfast with carbohydrate 6g. Results showed that blood glucose / immunoreactive insulin (IRI) at 0-30 min on average changed 88.0-130.6 mg/dL/5.1-46.5 µU/mL for GTT, and 90.1-86.3 mg/dL/4.8-12.5 µU/mL for MTT. IRI responses in GTT and MTT were calculated by 3 methods, which are i) increment (delta), ii) Area Under the Curves (AUC), iii) Multiple (times) of basal value. Both data from GTT and MTT showed significant correlation in i) and ii) ($p<0.05$), but not significant in iii) ($p=0.07$, $n=9$). These results suggested that insulin secretion in MTT would be enough and relatively excessive for 6g of carbohydrate, leading to relatively decreased glucose at 30 min. Current analyses methods will become some reference for future development of diabetic research.

Keywords: Area under the curves, Glycemic index, Meal tolerance test, Low carbohydrate diet, Japanese LCD promotion association.
Abbreviations: AUC: Area Under the Curves, GI: Glycemic Index, MTT: Meal tolerance test, LCD: Low Carbohydrate Diet, JLCDPA: Japanese LCD promotion association, IRI: Immunoreactive insulin, OGTT: Oral glucose tolerance test

Introduction

Across the world, diabetes and its complications have brought significant medical and economic impact [1]. The targets of the influence include individuals, their families, associations, health systems and nations. Diabetes has been more prevalent in developing and developed countries [2]. The important aspects of diabetes would be the presence of chronic complications such as microvascular and macrovascular disorders [3]. From pathophysiological point of view, pre-prandial and post-prandial hyperglycemia have been the main cause of various harmful signs and symptoms.

As to diabetic therapy, fundamental principle has been adequate nutrition. Formerly, Calorie Restriction (CR) was rather popular. However, recent recommended treatment would be Low Carbohydrate Diet (LCD), and it has been more prevalent in health care and medical region [4]. Successively, the evidence of LCD has been reported by several investigators, including meta-analysis of randomized controlled trials [5,6]. In recent years, the beneficial efficacy of LCD has been rather well-known [7].

In contrast, authors and co-researchers have started LCD first in Japan [8]. We continued diabetic practice and research, and reported clinical effects of LCD [9]. Through social LCD movement by Japanese LCD Promotion Association (JLCDPA), we have proposed practical tips for LCD. They are petite-LCD, standard-LCD, super-LCD associated with 40%, 26%, 12% of carbohydrate content, respectively [10]. In addition, our research team has reported various achievements, such as daily profile of blood glucose, elevated ketone bodies, Continuous Glucose Monitoring (CGM), Meal Tolerance test (MTT), and others [11,12].

Regarding the research for MTT, we have already proposed carbo-70 meal test [13]. It uses traditional Japanese breakfast with CR meal, including carbohydrate 70g [14]. It depends on standard macronutrient ratio of nutrition guideline of Japan Diabetes Association (JDA) [15]. In recent clinical practice, LCD treatment has been more highly evaluated from various reports [12,16]. Consequently, we have tried a pilot study of MTT using LCD breakfast with carbohydrate 6g. In this study, we have compared the response of insulin for MTT and 75g Oral Glucose Tolerance Test (OGTT), and describe the results and some discussion.

Subjects and Methods

Enrolled subjects were healthy medical staffs in the hospital, who were 5 males and 4 females with 22-30 years old. They did not have remarkable diseases so far. Their BMI were all normal. Methods included two examination. One is 75gOGTT with the measurement of glucose and insulin (immunoreactive insulin, IRI). Another exam is MTT with the breakfast of LCD. It has 300 kcal with nutrition element of protein 13g, fat 24g, carbohydrate 6g. Blood glucose and IRI were also measured similarly.

There tests were performed for 9 same subjects with a week interval. The measurements included blood glucose at 0, 30 and 120 min and IRI at 0 and 30 min. The response of IRI for carbohydrate loading were calculated by three methods. They are i) increment (delta, ⊿) of IRI, ii) Area Under the Curves (AUC) of IRI, iii) multiple (times) number of IRI to the basal value. In this study, data were obtained as glucose and IRI values. Correlation between related factors were investigated. The significant correlation was judged to be present at the border as p<0.05.

Ethical Considerations

This investigation was basically performed with the ethical principles on the Declaration of Helsinki. Moreover, some presentation has been conducted by the Ethical Guidelines for Research for Humans, with the Good Clinical Practice (GCP). The consideration for the protection of human rights was also present. "Ethical Guidelines for Epidemiology Research" was also applied as the guideline. This concept was proposed by the Ministry of Health, Labor and Welfare and the Ministry of Education, Culture, Sports, Science and Technology in Japan.

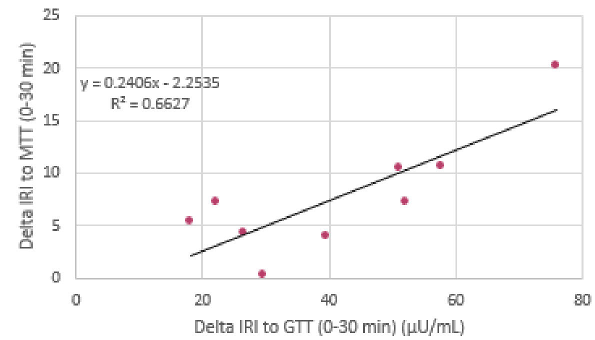
The author and collaborators established the ethical committee in the hospital. The committee included several experts including physician, nurse, pharmacist, dietician and legal-specialized person. For current study, the discussion for the study was performed, and it has decided with all agreements. For enrolled subjects, informed consents and written documents were obtained from all subjects. This study has been registered by National University Hospital Council of Japan (ID: #R000031211).

Results

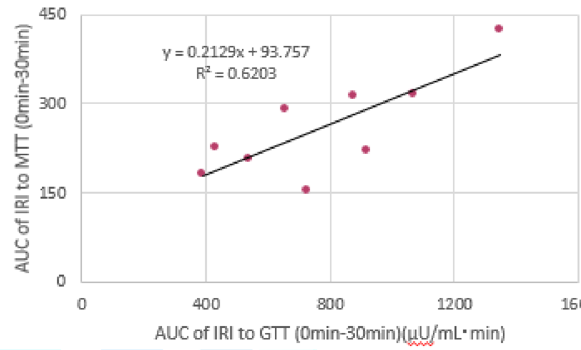
Responses of glucose and IRI for GTT and MTT were summarized in **Table 1**. It shows the data by mean ± SD and median. Correlation of Delta IRI between GTT and MTT was shown in **Figure 1a**. The value R2 equals 0.663, then r=0.814. It means very strong correlation. Further, correlation of AUC of IRI between GTT and MTT was shown in **Figure 1b**. The value R2 equals 0.620, then r=0.787. It also means very strong correlation. In contrast, correlation of IRI response times between GTT and MTT was shown in **Figure 1c**. The value R2 equals 0.393, then r=0.626. In this case, P value was calculated as 0.071. It means that there is not significant correlation between them.

		Time (min)	Mean ± SD	Median	Units
GTT-75g	Glucose	0	88.0 ± 8.8	88	mg/dL
		30	130.6 ±24.3	131	mg/dL
		120	83.1 ± 16.6	77	mg/dL
	IRI	0	5.1 ± 1.7	4.8	µU/mL
		30	46.5 ± 19.9	44	µU/mL
MTT-6g	Glucose	0	90.1 ± 9.0	93	mg/dL
		30	86.3 ± 9.6	84	mg/dL
		120	84.4 ± 9.9	90	mg/dL
	IRI	0	4.8 ± 2.0	4.8	µU/mL
		30	12.5 ± 5.3	10.2	µU/mL

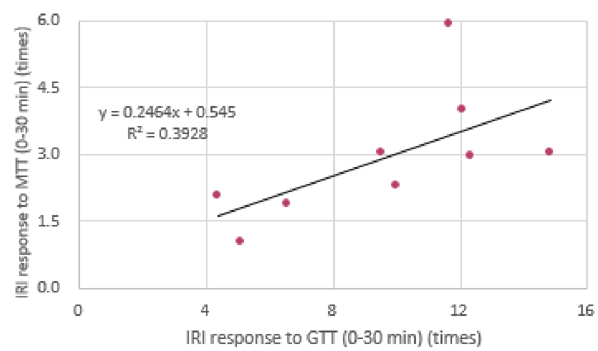
Table 1: Results of GTT and MTT.



1a: Correlation of Delta IRI



1b: Correlation of AUC of IRI



1c: Correlation of IRI response times.

Figure 1: Correlation of IRI responses between GTT and MTT.

Comparison of 3 statistic methods for investigating the correlation between IRI responses for GTT and MTT was summarized **(Table 2).** They are increment (Delta, ⊿), Area Under the Curve (AUC), and multiple (times) number. As the results, former two, delta and AUC showed significant correlations with P value 0.007 and 0.012, respectively. Latter method (multiple) showed that correlation coefficient was 0.626 and P value was 0.071. This value (p=0.071) is close to the borderline of significant level (p<0.05).

Discussion

American Diabetes Association (ADA) showed the official comment. Among the macronutrients of carbohydrate, protein, fat, only carbohydrate influence the blood glucose level [17]. The authors have been involved in LCD clinical and research for years [13,18]. Among them, factors related to elevated blood glucose include i) intake of the amount of carbohydrate, ii) glycemic index (GI) [19], iii) insulin secretion [20]. From this point of view, current pilot study seems to be meaningful.

Statistic Methods	sample number	Correlation coefficient	t-value	P value bilateral	t (0.975)	95% lower limit	95% upper limit
Increment (Delta, ⊿)	9	0.814	3.708	0.0075	2.364	0.326	0.959
Area Under the Curve (AUC)	9	0.787	3.381	0.0117	2.000	0.258	0.953
Multiple Number	9	0.626	2.128	0.0708	2.364	0.064	0.911

Table 2: Comparison of 3 statistic methods.

Firstly, the medical concept of Glycemic Index/Glycemic Load (GI/GL) was proposed by Jenkins et al., in which there are different carbohydrates for influencing potential metabolic responses with different Glycemic Responses (GR) [21]. Regulation for human satiety seems to have complex related mechanisms, such as insulin, glucagon-like peptide 1 (GLP-1), leptin, ghrelin, Cholecystokinin (CCK), and so on [22].

Concerning the study of GI and GR, 73 reports out of 445 articles were selected by systematic PubMed search. The result showed that GI of a food or diet is unlikely to be linked to disease risk or health outcomes. For the predictors of health benefits, food patterns would be more related to dietary guidance [23].

In the case of rice, GI may vary remarkably by the condition of rice, cooking and processing method from the data of 7-132 [24]. In addition, postprandial increases of glucose and IRI are reduced with the presence of protein [25].

In current study, the subjects were young and healthy, and blood glucose and insulin responses to 75g OGTT were found as expected. MTT was conducted using an LCD breakfast containing carbohydrate 6g. As a result, significant insulin secretion was observed and the blood glucose at 30 min tended to be lower than 0 min, which was impressive finding. This suggested that sufficient amount of insulin would be secreted from the β cells of the pancreas.

For 9 subjects of this study, insulin secretory pattern was checked in detail. In 6 subjects, additional secretory phase I seemed to be 2 to 3 times more than the basal secretion. It is thought that this insulin secretion decreased the blood glucose at 30 min, and that its efficacy for carbohydrate 6 g was fully covered and exceeded. In 1 subject, the first-phase insulin was low (1.03 times) at 30 min, but abrupt and more than twice secretion of insulin was suggested to be present at 15 to 25 minutes just after intaking LCD meal [26].

As a reference, there is a breakfast formula for MTT, which has 56g of carbohydrate [27]. It covers three main macronutrients with carbohydrate 50%, fat 35%, protein 15% and 450 kcal. This is a trial of international standard model for nutritional research and practice [27]. Another protocol meal for MTT is high-protein Boost-HP. It contains protein 15g, fat 6g, carbohydrate 33g, 237 ml with the nutritional balance as 25:20:55 of PFC ratio [28]. In recent study, subjects ingested 6 mL/kg of Boost meal solution for MTT with maximum 360 mL [29].

Among our diabetic research, there was a report of MMT with carbohydrate 70g [13]. By standard CR formula of Japan Diabetes Association (JDA), we prepared useful breakfast including rice, egg, vegetable in Japanese style [15]. The study included 48 patients with T2DM, which were categorized by HbA1c level into high, middle and low groups. Middle group showed the following data: HbA1c 7.8%, blood glucose was from 166 mg/dL to 203 mg/dL, IRI was from 4.5 μU/mL to 13.5μU/mL during 0 to 30 min by loading of Carbo-70 formula meal [13,21].

From the results of this study, both of insulin responses for GTT and MTT showed significant correlation for 75g and 6g of carbohydrate. When the increased level of insulin secretion was examined by three methods, almost the same results were obtained by delta and AUC methods. By the times ratio method to the basal value, correlation coefficient was r=0.07, which did not satisfy <0.05 level at present. However, this pilot study includes only 9 cases, then, it is expected that a significant difference will be present as the number of cases increases.

We previously investigated AUC for insulin secretion in diabetes [30]. Carbo70 loading was performed on 42 cases of T2DM, and the insulin response was examined in 0 to 30 minutes. Patients was divided into 3 groups according to their severity, and the median HbA1c was 6.3%, 7.9% and 9.8%, respectively. Compared with the M value, the data of three groups were 0.17, 0.10 and 0.10 in the Delta method, but the data distribution were separated in the AUC method as 5.2, 2.9 and 1.9. Correlation with the data of M value showed that y = 0.6147x-0.336, R^2 = 0.2838, r = 0.53 in Delta method, and y = 13.965x-0.306, R^2 = 0.5375, r = 0.73 in AUC method. Thus, r value was higher in AUC method. From the above, it was suggested that the AUC method is superior to the Delta method [28]. The reason for this would be that the secretion of hormones seems to show smaller error when calculated as a whole [30].

Secondly, there are two phases of insulin secretion in response to the intake of carbohydrate, which are the first phase (I) and the second phase (II) [31]. Normal people have additional insulin secretion as soon as their blood sugar starts to rise. This is called the first phase reaction, and the originally pooled insulin is secreted for 5 to 10 minutes to prevent sudden postprandial hyperglycemia during carbohydrate intake [26]. Then, the beta cells of the pancreas produce a rather small and persistent secretion of insulin called the phase II response. This covers the rest of the glucose in the diet. In other words, the second phase of insulin secretion continues while ingesting glucose.

In the light of our diabetic practice for long, authors et al. found that some patients showed reduced or missing the first phase of additional insulin secretion. There is probably a group of people who have inferior function of the beta cells, and are prone to diabetic states. As mentioned above, this study analyzed the response of insulin to GTT and MTT. The limitations of this study are insufficient number of cases and undetected associated factors. Future research under various conditions would be necessary.

In summary, this pilot study examined the secretory response of insulin to carbohydrates in three ways. As the number of subjects increase, significant correlations are supposed to be present. A variety of research design will be expected to bring further development in the future.

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