



## Blood Glucose and Insulin Values on Daily Profile, M Value and Meal Tolerance in Patients with Type 2 Diabetes Mellitus (T2DM)

Takehisa Y<sup>1</sup>, Bando H<sup>2\*</sup>

<sup>1</sup>Hakuai Memorial Hospital, Heisei Medical Welfare (HMW) group, Tokushima, Japan

<sup>2</sup>Tokushima University / Medical Research, Tokushima, Japan

Corresponding Author: **Hiroshi BANDO, MD, PhD, FACP** [ORCID iD](#)

**Address:** Tokushima University / Medical Research, Nakashowa 1-61, Tokushima 770-0943 Japan.

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### Abstract

**Background:** Authors and collaborators have continued medical practice in the Heisei Medical Welfare (HMW) group for long years for mainly two areas, extensive care for the elderly and diabetes research. From both of them, the current research was held on the daily profile of glucose and insulin for patients with type 2 diabetes mellitus (T2DM).

**Subjects and Methods:** Cases were 6 T2DM patients in admission, with ages  $67.5 \pm 12.7$  years, diabetes duration 9.5 years. Methods included a daily profile of glucose and insulin for seven times per day, Morbus (M) value, Meal Tolerance Test (MTT) using breakfast with 70g carbohydrate, insulinogenic index (IGI)-2 hours, various correlations among HbA<sub>1c</sub>, M value, Area Under the Curve (AUC) of glucose and insulin.

**Results:** Cases showed average values of HbA<sub>1c</sub>  $8.4 \pm 0.7\%$ , glucose 197 mg/dL, M value 111. Glucose and IRI levels increased during 0700-0900h with 154-258 mg/dL and 13.8-54.3  $\mu$ U/ml. There was a significant correlation between Glucose- $\Delta$ AUC and M value ( $p < 0.05$ ).

**Discussion:** Daily profile of glucose and insulin showed a similar manner, suggesting post-prandial glucose influence due to carbohydrate intake. When studied cases increase, significant correlations among M value, HbA<sub>1c</sub> and glucose-AUC seem to be found. This report hopefully becomes a reference for future diabetic research.

### Keywords

Daily Profile of Blood Glucose and Insulin, Meal Tolerance Test (MTT), Insulinogenic Index (IGI), Area Under the Curve (AUC), Morbus (M) Value, Heisei Medical Welfare (HMW)

### Introduction

Diabetes is known to be one of the crucial non-communicable diseases (NCDs) across the world and has given various influences socially and medically [1]. It may cause not only microangiopathy involving neuropathy, retinopathy, nephropathy but also macroangiopathy in the brain, heart, legs [2]. There

are some standard guidelines for diabetes. One is the 2019 “Consensus Statement by the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) on the Comprehensive Type 2 Diabetes Management Algorithm” [3], and another is the American Diabetes Association (ADA) Standards of Medical Care in

Diabetes—2020 [4].

From the viewpoint of glucose variability, there is a concept of glucose ranges and targets [5]. The ideal target range has been indicated the international consensus on time in range (TIR). It has been provided from the detailed investigation of continuous glucose monitoring (CGM) metrics and considerations from the clinical interpretation and care [6]. In order to develop these metrics, there are some standardized reports recommending a visual manual with the ambulatory glucose profile (AGP) [6]. Various data from these analyses may help both the provider and patient to bring adequate treatment decisions. Consequently, this progress can result in diabetes management more useful for nutrition therapy, physical activity, preventing hypoglycemia, adjusting medications [7].

The authors and collaborators have been involved in two areas, diabetes research and extensive care research for the elderly. Firstly, authors and collaborators have continued medical practice for years in the Heisei Medical Welfare (HMW) group, which has been one of an international medical organization [8]. Specifically, in Japan, there are complex medical facilities in Tokushima, Tokyo, and other cities, as well as rehabilitation facilities in Indonesia, associated with more than 10,000 beds and 15,000 medical staff [9]. The philosophy and purpose of HMW would be to save all people, by providing proper acute care (PAC) and sub-acute care (SAC). A variety of patients have a wide range of health problems such as non-communicable diseases (NCD), diabetes mellitus, hypertension, dyslipidemia, chronic renal diseases (CKD), frailty syndrome in the elderly, and dementia. We have also reported on the practice of integrative medicine with music therapy as a wide range of medical care [10,11].

Secondly, for diabetes, we have already reported diurnal fluctuations in blood glucose [12,13]. Among them, comparative studies of calorie restriction (CR) and low carbohydrate diet (LCD) have been conducted [13,14]. When changing the meal from CR to LCD, the daily profile of glucose drops dramatically from that day [13,15]. Among them, we have reported on clinical investigations, especially for diabetic patients [9,16].

The authors have recently conducted studies on glycemic and insulin secretory dynamics from a pathophysiological aspect for meal tolerance test (MTT) in diabetic patients [17-19]. For this aspect, the dynamics of blood glucose and insulin on the diurnal variation of the day were investigated, with the estimation of a useful biomarker as Morbus (M) value [17,20].

In our broad clinical practices mentioned above, our research group has now investigated the daily profiles of glycemic and insulin values with pre- and post-prandial status in diabetic patients. In this article, we will report the results of the study and give some discussion.

## Subjects and Methods

### Subjects

Subjects in this study included six patients with T2DM in the admission of Hakuai Memorial Hospital, Tokushima, Japan. The background of the subjects is summarized and shown in Table-1.

### Methods

There are some purposes and/or protocol of this study as follows: a) The daily profile of blood glucose and immunoreactive insulin (IRI) level were measured 7 times a day. They include pre-prandial and post-prandial timings at three meals and night, b) From the changes of daily blood glucose, Morbus value was calculated that means the integral concept of elevated blood glucose in average and increased mean amplitude of glycemic excursions (MAGE), c) Meal Tolerance Test (MTT) was conducted using breakfast, which includes 70g of carbohydrate from standard Japanese breakfast with rice, egg, fish, salad and miso soup, d) From the changes of blood glucose and IRI after 2 hours of breakfast, Insulinogenic Index (IGI) (2 hours) was calculated.

### AUC Study:

For pathophysiological evaluation for glucose and IRI, the method of Area Under the Curve (AUC) has been used [21]. Glucose AUC can be measured and calculated by the multiplication of glucose value and time [22,23]. In the current study, data of glucose values are obtained 7 points from 0700h to 2100h, and

the Glucose-AUC was calculated. Furthermore, we have also used Glucose-delta AUC (Glucose- $\Delta$ AUC). It means the incremental AUC from the point at 0700 AM, which equals total Glucose-AUC minus baseline-AUC. Similarly, IRI-AUC and IRI-delta AUC (IRI- $\Delta$ AUC) were also calculated.

In our protocol of c) and d), we adopted and compared two methods. The former means the incremental values of glucose and IRI. It is expressed as Delta ratio of IGI for 2 hours, which can be calculated as (IRI at 2 hours - IRI at 0min) ( $\mu$ U/mL) / (Glucose at 2 hours - Glucose at 0min) (mg/dL). The latter means the comparison of the total AUC of glucose and IRI. It is expressed as AUC Ratio of IGI for 2 hours, which can be calculated as (AUC-IRI for 0-2 hours) ( $\mu$ U/mL x h) / (AUC-glucose for 0-2 hours) (mg/dL x h) [24].

#### M Value Study:

In diabetology, Morbus (M) value is a useful biomarker for research of glucose variability. M value includes two valuable meaningful data. The first is the value of the average blood glucose a day, and the second is the width of the blood glucose fluctuation, which is known as the mean amplitude of glycemic excursions (MAGE) [25-27]. M value has both meanings and can evaluate the general degree of the glucose variability in the diurnal rhythm.

Consequently, the M value can be calculated as one numerical value including two valuable perspectives. The former is the level of increased glucose on average, and the latter is the degree of elevated swinging glucose of the variability. On applying the following mathematic method, the M value is calculated for the equation by the logarithmic transformation method. Concerning clinical significance, M value means the degree of the increased deviated glucose from the ideal level of glucose variability in the glucose profile [26-28].

The method of calculation of M value includes three steps. The first is the fundamental equation, which is  $M = M^{BS} + M^W$ . M value is described as the total value of  $M^{BS}$  and also  $M^W$ . The second is the  $M^W$ , which can express (max blood glucose - min glucose)/20. The

last one showed that  $M^{BS}$  is the mean level of MBSBS. By summarizing these data into an equation, MBSBS is the individual M-value for each blood glucose, that is calculated as (absolute numerical value of  $[10 \times \log(\text{blood glucose level}/120)]^3$  [26-28]. The numerical number 120 means that the ideal level of glucose may be about 120 mg/dL.

Generally speaking, glucose variability has been estimated as the increased level of M value. The obtained results of M value have been evaluated in the following: i) the usually standard normal range would be less than 180, ii) the borderline width would be 180 and more than 180 plus less than 320, and iii) abnormal range would be 320 and more than 320.

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

#### Statistical Analysis:

In the current study, the number of subjects was small (n=6), which means the pilot study. Before analyzing the data, a fundamental investigation was conducted. Since all items have a statistically normal distribution, all analyses were subjected to the Pearson correlation test [29].

#### Ethical Considerations:

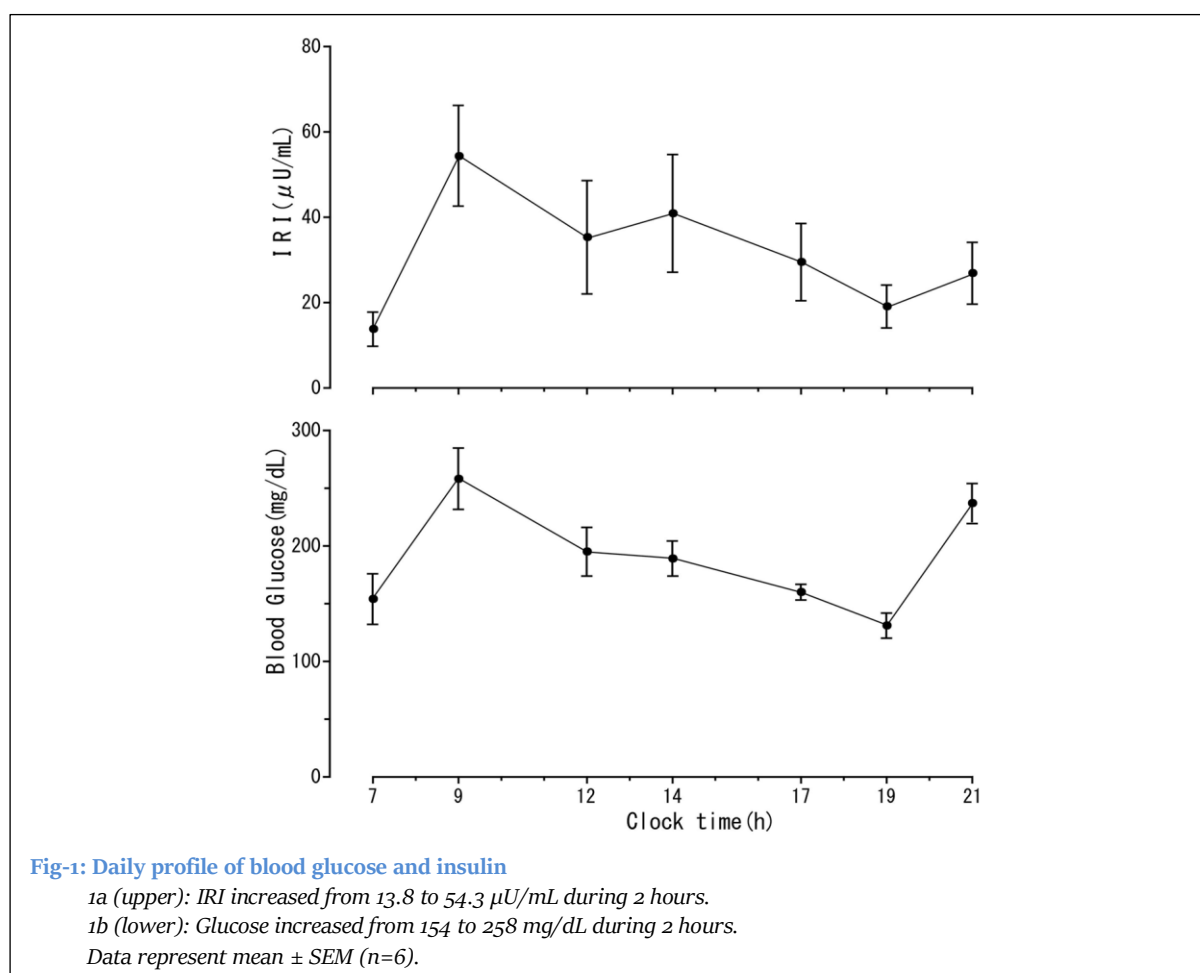
The current study was basically performed along with the Declaration of Helsinki (revised at the 2013 WMA Fortaleza General Assembly). Further, the additional comment was performed along with the ethical guidelines for human-based medical research (notification by Ministry of Education, Culture, Sports, Science and Technology [MEXT] and Ministry of Health, Labour and Welfare [MHLW]). The content of the current test was fully explained to the patients in advance. We have obtained the written document agreements from all patients. This study was discussed in the ethical committee, where several professionals attended and approved, including physicians, nurses, pharmacists, nutritionists, and a person of legal specialty. This research has been registered and performed along with the National University Hospital Meeting (ID: #R000034009).

## Results

In the current study, the results for 6 cases are shown in Table-1. Obtained levels of mean  $\pm$  standard deviation (SD) were as follows: ages  $67.5 \pm 12.7$  years old (the median 64.5 yo., and M/F=3/3). Duration of diabetes is 9.5 years on average and 6.0 years in the median. HbA<sub>1c</sub>  $8.4 \pm 0.7$  years (median 8.3%). Regarding the average blood glucose from 7-point measurement a day, the result showed 197 mg/dL on average ranging from 171.7 mg/dL to 233.3 mg/dL. Furthermore, there were several results concerning glucose and insulin-related data were obtained.

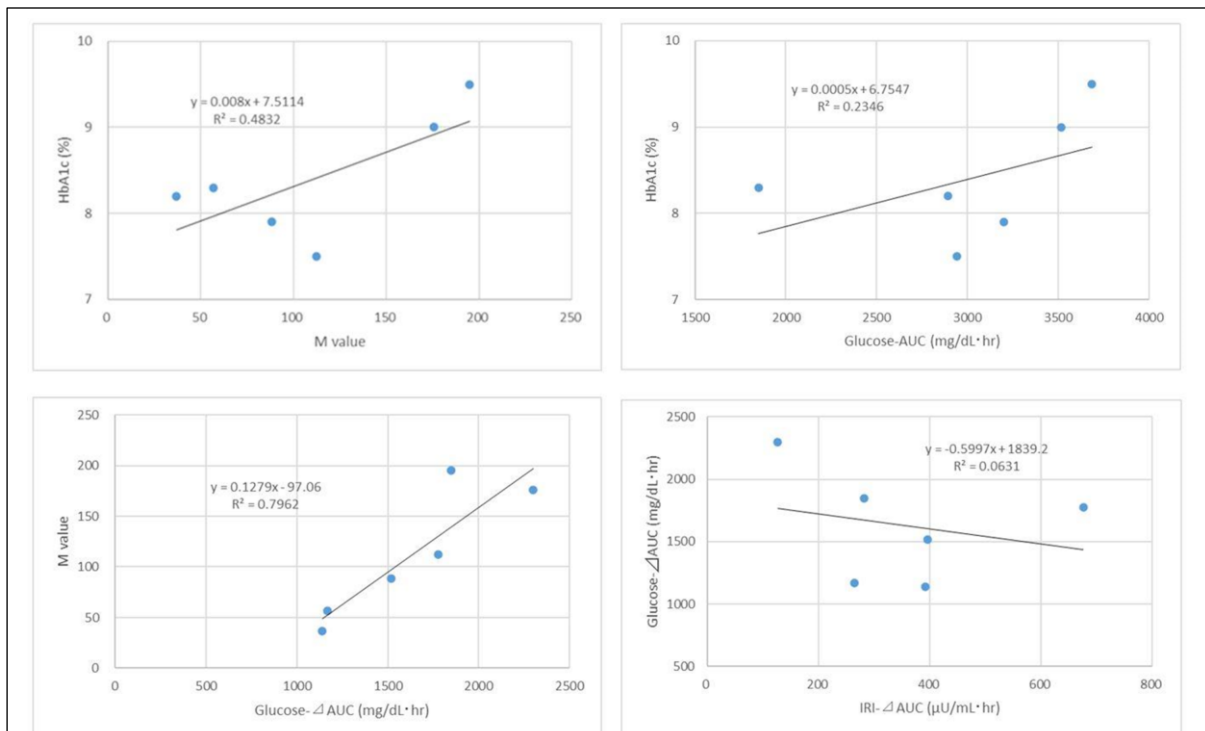
The daily profile of glucose and IRI was shown in Fig-1. Blood glucose and IRI levels increased from

0700h to 0900h, with 154 to 258 mg/dL and 13.8 to 54.3  $\mu$ U/ml on average. From 0900h to 2100h, both data were found to be moved in similar manner. Several kinds of correlations among HbA<sub>1c</sub>, M value, the AUC changes of blood glucose, and IRI were investigated (Fig-2). These results of the correlations between 2 factors are from a small number of cases (n=6). There were 4 correlations shown as follows: a) correlation between M value and HbA<sub>1c</sub> is  $p=0.125$ , not significant (Fig-2a), b) correlation between Glucose-AUC and HbA<sub>1c</sub> is  $p=0.330$ , not significant (Fig-2b), c) correlation between Glucose- $\Delta$ AUC and M value is  $p=0.016$ , significant (Fig-2c), d) correlation between IRI- $\Delta$ AUC and Glucose- $\Delta$ AUC is  $p=0.631$ , not significant (Fig-2d).



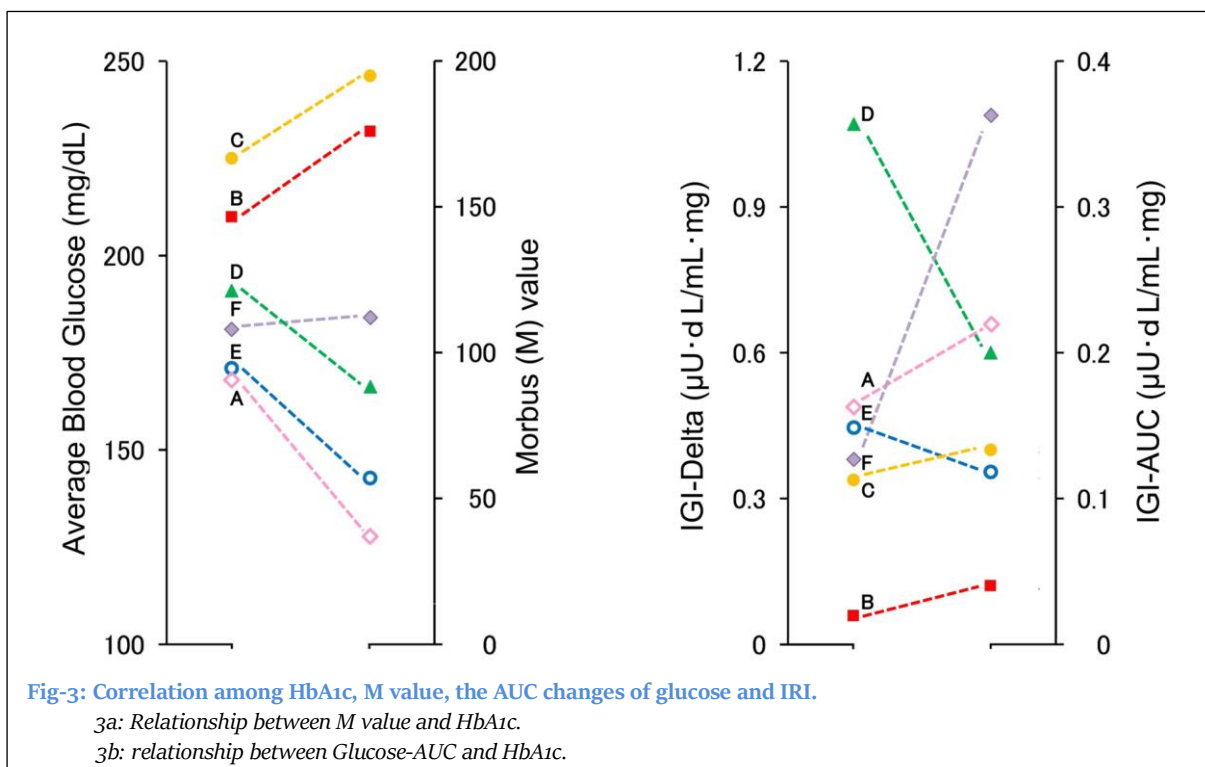
Further evaluation of the values of blood glucose and IRI during 0700h-0900h was conducted. We investigated the relationship between the average glucose level and M value (Fig-3a) and between the IGI-delta method and IGI-AUC method (Fig-3b). The

former revealed a close relationship (Fig-3a). For the latter, case D and F showed rather larger different data by two methods of calculation (Fig-3b).



**Fig-2: Correlation among HbA1c, M value, the AUC changes of glucose and IRI.**

- 2a: Correlation between M value and HbA1c ( $p=0.125$ , n.s.,  $n=6$ )
- 2b: Correlation between Glucose-AUC and HbA1c ( $p=0.330$ , n.s.,  $n=6$ )
- 2c: Correlation between Glucose-ΔAUC and M value ( $p=0.016$ , significant.,  $n=6$ )
- 2d: Correlation between IRI-ΔAUC and Glucose-ΔAUC ( $p=0.631$ , n.s.,  $n=6$ )



**Fig-3: Correlation among HbA1c, M value, the AUC changes of glucose and IRI.**

- 3a: Relationship between M value and HbA1c.
- 3b: relationship between Glucose-AUC and HbA1c.

## Discussion

In recent decades, the research on CR and LCD has expanded in the study of diabetes. LCD was advocated by Atkins and Bernstein and spread to Europe and the United States [30,31]. In Japan, Dr. Ebe in our research group had started LCD for the first time [32] and we have been enlightening how to practice petite-LCD, standard-LCD, and super-LCD [33].

CR includes higher carbohydrate and raises postprandial blood glucose [34]. On the other hand, LCD has lower carbohydrate and suppresses the rise in postprandial glucose [35]. In other words, it is important to reduce the response of postprandial glucose and insulin to meals [36]. Consequently, studies on diurnal fluctuations of glucose and insulin have been conducted. As a method, the pathophysiological status can be grasped by examining

the AUC or  $\Delta$ AUC of glucose and insulin for 24 hours [37]. Studies on total AUC and  $\Delta$ AUC for blood glucose and IRI in 0-3 hours were investigated after ingesting several foods [38]. With these research methods, detailed responses for glucose and insulin can be taken for various pathophysiological states.

In the current study, diurnal fluctuations in glucose and insulin levels were measured in 6 middle-aged and elderly diabetic patients. The correlations among mean blood glucose, HbA1c, M value, AUC value,  $\Delta$ AUC value, etc. were investigated. Furthermore, AUC and  $\Delta$ AUC in glucose and insulin during 0700h and 0900h were measured and analyzed. Regarding the patient background, the mean HbA1c was 8.4% and the mean blood glucose was 197 mg/dL. Then, these subjects were estimated to be in rather a moderate degree of diabetes mellitus (**Table-1**).

Case		HbA1c	Glucose related Profile				Insulin Profile		
Case	Age/Sex	DM Hx (yr)	HbA1c (%)	Glu-Ave (mg/dL)	Glu-AUC (mg/dL·hr)	Glu- $\Delta$ AUC (mg/dL·hr)	M value	IRI-AUC ( $\mu$ U/mL·hr)	IRI- $\Delta$ AUC ( $\mu$ U/mL·hr)
A	49 M	7	8.2	171.7	2892	1140	37	566	392
B	83 M	27	9.0	217.0	3514	2300	176	176	126
C	81 F	1	9.5	233.3	3684	1848	195	468	282
D	63 F	4	7.9	194.8	3200	1520	88	514	396
E	64 F	5	8.3	177.3	1850	1170	57	344	264
F	65 M	13	7.5	187.7	2940	1776	112	1056	676
<b>Average</b>	67.5	9.5	8.4	197.0	3180	1826	111	520.8	355.4

The characteristic of diurnal variation in blood glucose and IRI seemed to be that the movements of both graphs are generally similar (**Fig-1**). For pre-prandial and post-prandial points of breakfast, glucose and IRI were clearly elevated. These results were observed in all 6 cases. One of the reasons may be the process that they had breakfast after persisting overnight fast. On the other hand, those cases did not show a constant tendency for lunch and supper. The reason has not been clarified, but some possibilities are suggested, such as the difference in the both of absorption and digestion, the content of the meal with PFC ratio, the influence of breakfast to lunch including second meal phenomenon.

Among them, an increase in glucose and IRI has been found from 1900h to 2100h at night. The reason

for this is not clear, but glucose and insulin responses may differ between morning and night. Concerning this phenomenon, there was a recent report by Leung et al. [39]. Biological results of eating habits at night would be responsible for increased postprandial glucose response, compared with that at an earlier time in the day. According to the investigation on electronic databases, primary outcome markers were post-prandial glucose and IRI area under the curve (AUC) or  $\Delta$ AUC (incremental AUC, iAUC). This mechanism would lead to the well-known tendency that those who usually eat during the night apt to have a higher risk of metabolic situation including T2DM and cardiovascular disease (CVD) [39].

As regard to the detailed glucose fluctuation, there was rapid development due to CGM with new

technology [6]. From these accumulated data, the provider can determine the time in range (TIR) with the assessment of hyperglycemia, hypoglycemia, and glycemic variability. The standard TIR shows very high (>250 mg/dL), high (181-250 mg/dL), target range (70-180 mg/dL), low (54-69 mg/dL), and very low (<54 mg/dL). According to the published data, a strong correlation has been suggested between TIR and HbA1c value, such as a goal of 70% TIR aligning with an HbA1c of 7% from two prospective investigations [7,40]. A detailed study of glucose and insulin values would be expected for future study.

In the current report, several correlations were studied among HbA1c, M value, the AUC changes in blood glucose, and IRI (**Fig-2a** to **Fig-2d**). There was a significant correlation between Glucose- $\Delta$ AUC and M value (**Fig-2c**). In contrast, there was not a significant correlation between M value and HbA1c, and between Glucose-AUC and HbA1c (**Fig-2a** and **Fig-2b**). Current statistical studies have a small sample number (n=6), then they will presumably show significant correlations with a sufficient numerical number of subjects. In the research for the glucose variability, some biomarkers such as HbA1c, M value, AUC, and  $\Delta$ AUC (incremental AUC, iAUC) seem to be useful for investigating various correlations.

Regarding the relationship between blood glucose level and insulin secretion, the insulinogenic index (IGI) for 75 g OGTT has been prevalent for years [41,42]. Adjunct to the studies of CR and LCD, authors have proposed and studied IGI-carbo70 because the breakfast of the CR diet contains carbohydrate 70g [43]. Furthermore, we have tried research methods using C-peptide values instead of insulin as a biomarker and reported clinical usefulness [44].

Concerning the analysis of the meal tolerance test (MTT), the time period was not 0-30 min as a conventional method but 0-2 hours as a pilot study [14-16]. The result showed the intersection of case D and case F (**Fig-3b**), where the relative difference seemed to exist between the total area of IGI and the area of  $\Delta$ IGI. In previous studies, elder patients tended to show slower glucose and IRI responses with higher IRI values and glucose 2 hours after a meal [24].

Therefore, we analyzed AUC and  $\Delta$ AUC for glucose and IRI during 0-2h and analyzed several related data [23]. The result showed that the obtained distribution of M value was wider than the distribution of mean blood glucose, and then the difference can be clearly grasped [24]. In this way, even if the levels of HbA1c and mean blood glucose are nearly the same in many diabetic cases, the M value level could be clinically useful for detecting unstable glucose variability such as larger MAGE [17].

There are some limits to this study, and the following factors can be considered. Those are i) the number of cases is small, ii) both glucose and IRI are measured seven times per day, which are not sufficient times, iii) other possible influencing biomarkers are not measured at the same time. From this pilot study, it is positive and significant to obtain the theme or direction for the research in the future.

In summary, the diurnal variation of both glucose and insulin was measured against diabetic patients. Their AUC and  $\Delta$ AUC were calculated and obtained from the data, and the relationship among some biomarkers was investigated. This research will be hopefully served as reference data for research development in the future.

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## Conflict of Interest

All authors have read and approved the final version of the manuscript. The authors have no conflicts of interest to declare.

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